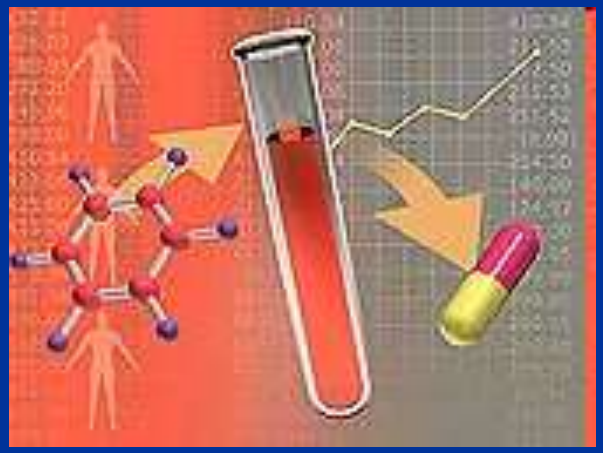
New Drugs: Their Development & Evaluation



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

New Drug Development

Concepts of

- 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 (Surviellence)

like covid-19 -> Idea was to develop a vaccine to target the Corona Virus.

Target therapy: like Cancer and targeting protein on cancer cells.

Clinical trials:
- specific phases
- Try drug on Animals then humans.

Aims of Therapeutic Evaluation

Most important concepts in pharmacology

- To assess **efficacy, safety & quality** of new drugs

benefit - Risk ratio

- To **expand indications** for the use of current drugs

↳ Good drugs maybe used for another diseases and that require more clinical trials and studies. استخدام في أمراض أخرى

- To **protect public health** ⇒ aim / Goal

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)**

We can drop the drug and execute it after a while, when showed a bad interaction or Risk higher than benefit.

Drug Development

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

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**

↳ Block β2 in Adrenergic receptor

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 / Vitro ⇒ Then collect and Analyse the data to go to the Next phase.
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

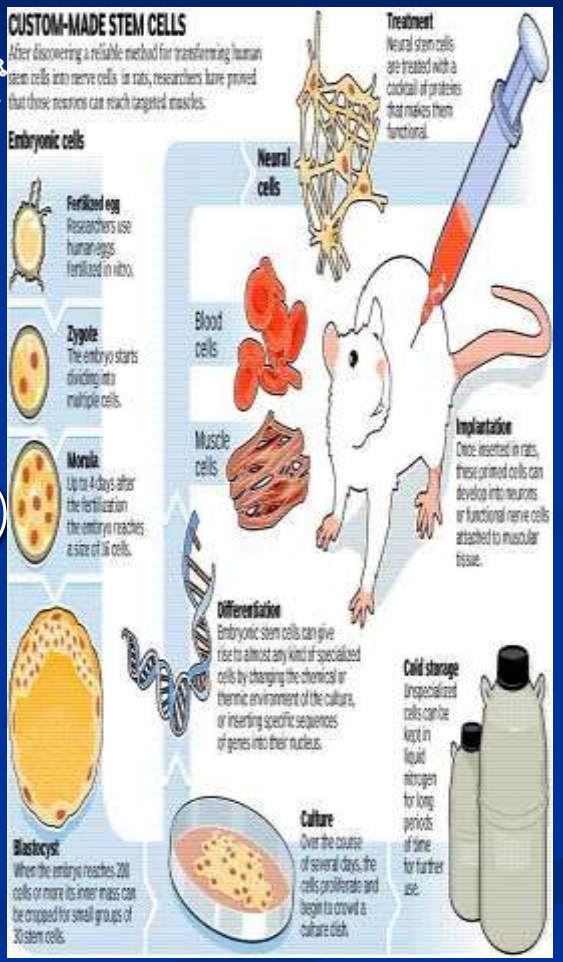
1. Pre-clinical Studies in Animals including:

B. Toxicological studies

@ after figuring out the dose and the dynamic + kinetic Relations

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

↳ for pregnant woman / female



2. Clinical Studies in Human

Clinical Trial Research Unit

- 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 [redacted]
  healthy volunteers (20-50 subjects)

ما عندهم أمراض!

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)

⇒ after we knew how the drug behaved.

- These are carried out on **a limited number of patients (50-300)** to:

diseased Patients Included ↖

- **General pharmacology of drug in patients**
- **Pharmacokinetics**
- **Pharmacodynamics**
- **Establish safety of drugs**
- **Assess potential therapeutic effects, comparison with placebo**

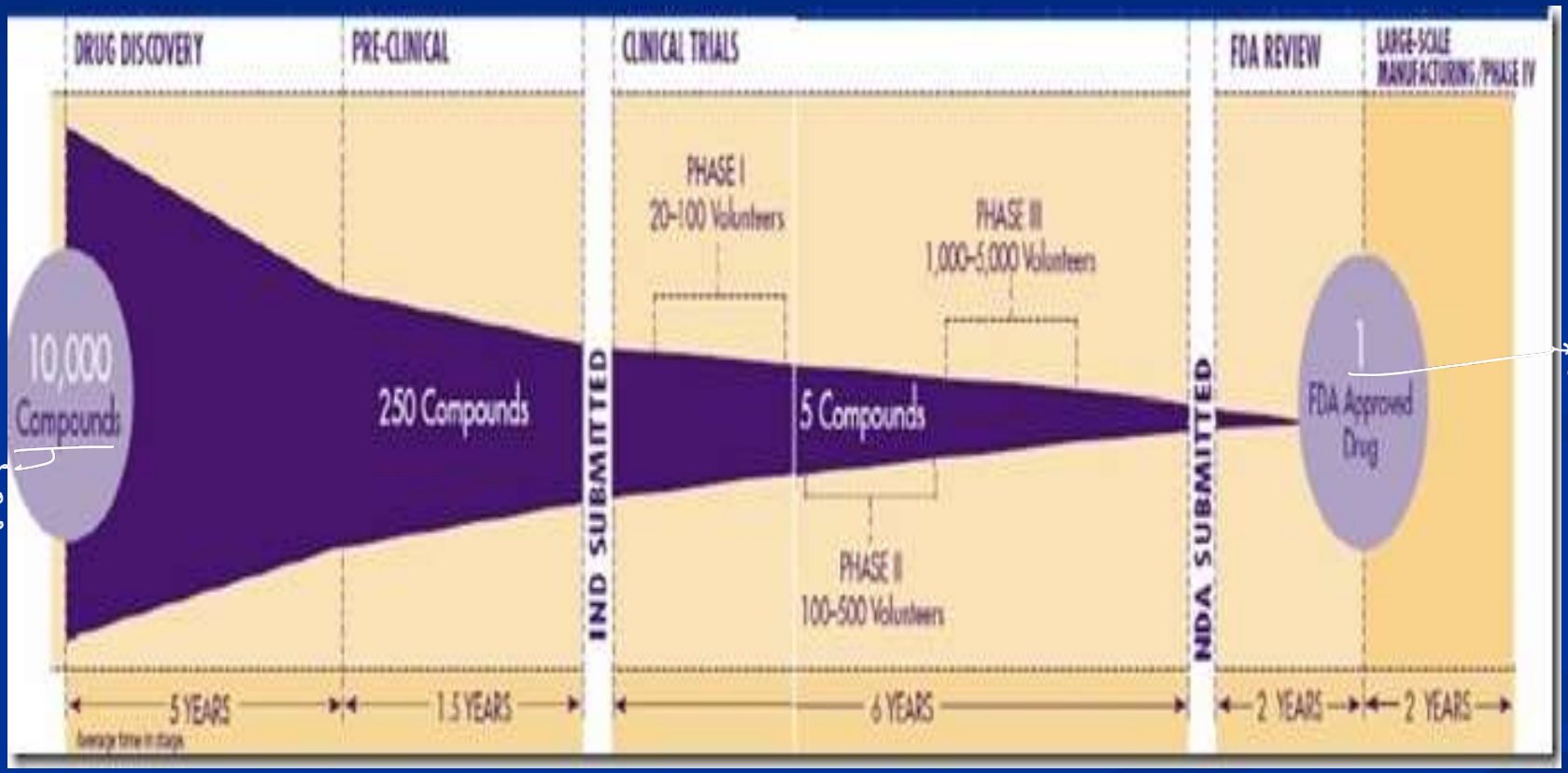
Phase 3 Studies (Therapeutic confirmation)

- **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)

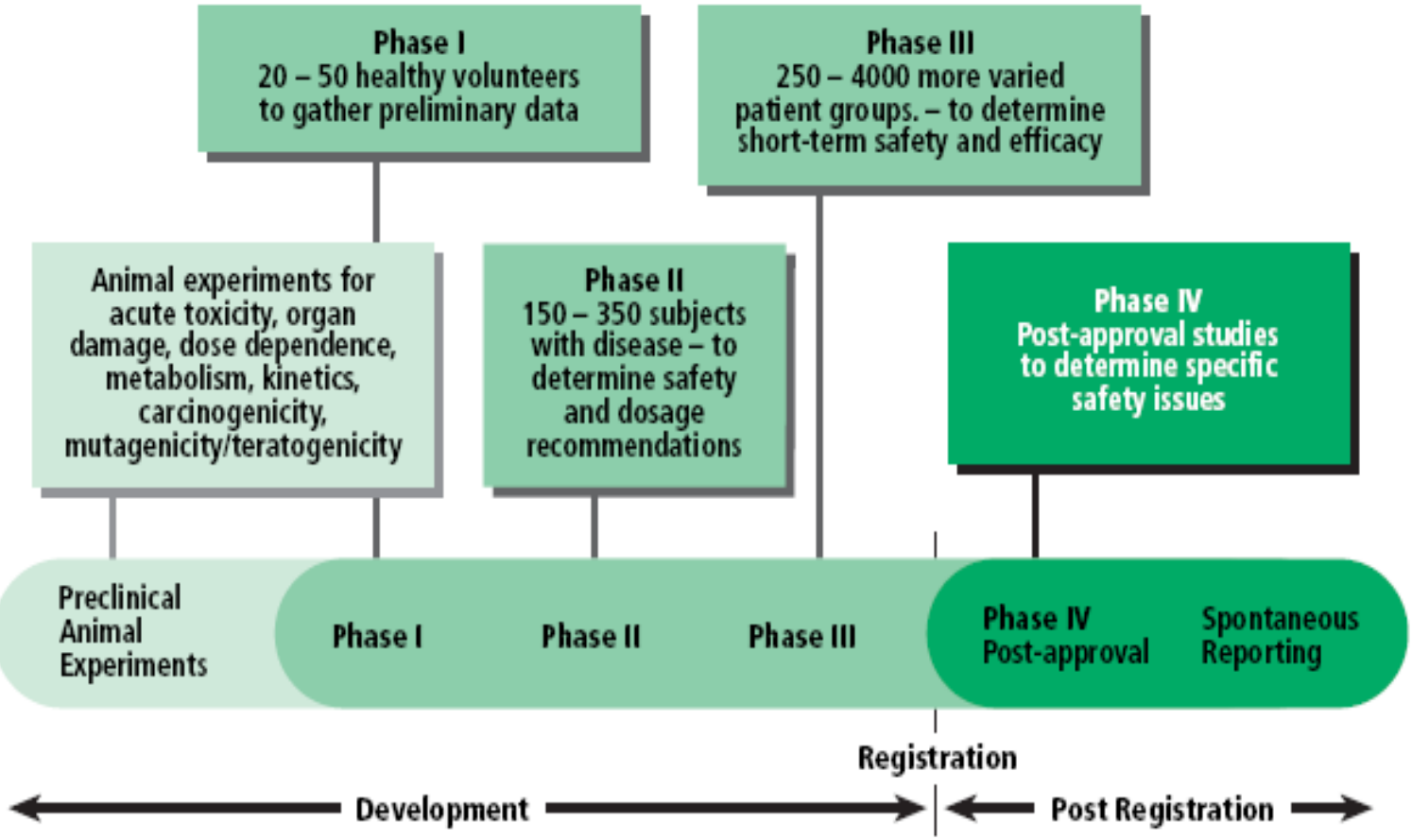
- These include **post-marketing surveillance (post-authorization studies) (2000- 10,000)** to look for possible **long term effects of drugs**
- **Long term efficacy & safety**

Phases of Drug Development



19

Figure 1 Clinical development of medicines



20

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 / cost is lesser for the patient.
- 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 / Target
- Definition of primary endpoints / The last step Analysis! / Extreme Analysis → Test the drug on short notice on new biomaker. → Faster Way, when you can't wait for years
- Method of analysis / reports / studies
- A protocol

Other factors when designing a trial:

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

استخدام تحليلات متوقعة/Predictions

Subjects included in the studies are either:

- Healthy normal volunteers or
- Patients ⇒ Specific

Patients excluded from clinical trials include:

- Children
- Pregnant women
- Mentally ill patients

⊗ After establishing if the drug is good on the Adult we may then try it on these groups of people.

Techniques to avoid bias

- **Randomization:** of Patients.

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

  ادخال عنصر الصدفة في اختيار وتقسيم المرضى للعلاج

- **Blinding** ⇒ The supervisor doesn't know if the patient had a placepo or the actual drug.

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**

Try drug A, then drug B, then compare the Results, Same patient

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

  → Inactive drug.

It is intended to:

- **Eliminate** observer or investigator **bias**
- Detect **non-pharmacological effects** of drugs **(placebo effects)** ⇒ Some patients can improve while there is only Mentally improvements.
- A **control** for statistical comparison

Conditions that do not require use of placebo

Mental comfort can't work on these patients.

- **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)

Not fully inert substance

- **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**

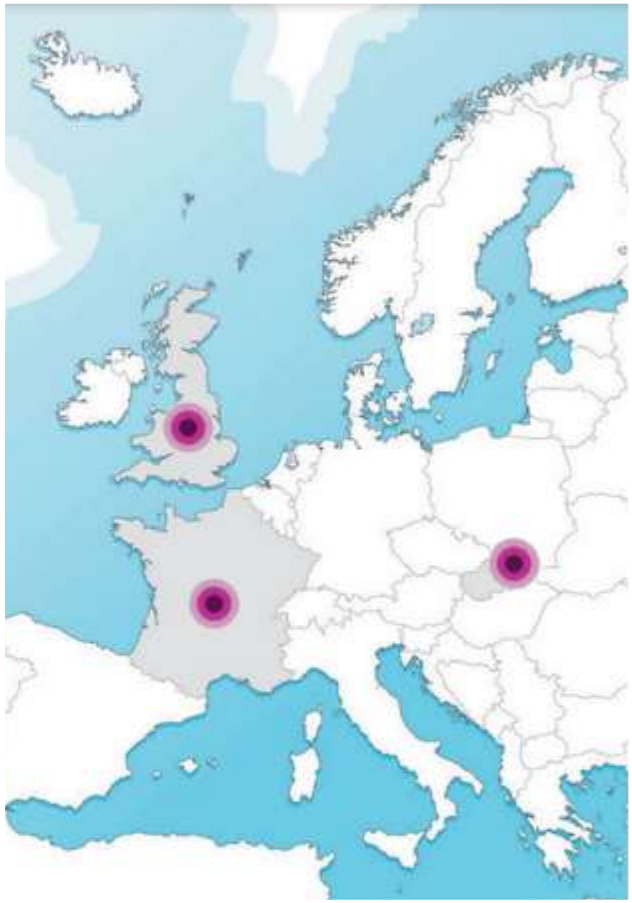
Recommendations are essential as a guide to doctors in clinical research:

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

⊕ Patient Retention ⇒ take good a care on the patients and keep up w/ them.

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, nitisinone
- Bone/muscle/cartilage markers
- Biochemistry profiles, metabolomics
- Genetics
- Acute phase reactants, cytokines

- **Urine:**
- HGA, tyrosine, nitisinone
- Bone & cartilage markers
- Metabolomics

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

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

- www.ClinicalTrials.gov