Unit IX – Problem 5 – Pharmacology: New Drug Development

- **Approaches for new drug invention and development:**
  - Identification of a new drug target.
  - Rational design of a new molecule (based on an understanding of receptors and mechanisms).
  - Screening for biologic activity of natural products and banks of previously discovered molecules.
  - Chemical modification of a known active molecule.
- **Stages of developing a new drug:**
  1. Idea or hypothesis.
  2. Design and synthesis of chemical molecule(s).
  3. Pre-clinical phase of evaluation on experimental (animals, cells, tissues and organs).
  4. IND (Investigational New Drug).
  5. Clinical phase of evaluation (clinical trials: phases I to III).
  6. NDA (New Drug Application)
  7. post-marketing surveillance (considered as phase-IV).
- **Pre-clinical testing:**
  - This is considered as phase (zero) and it aims to test for the toxicity of the drug in animals or in vitro (in tissues grown in culture dish).
  - This phase studies the following properties of the drug: pharmacokinetics (how does the body deal with the drug?), pharmacodynamics (what is the effect of the drug on the body?) and toxic/ harmful adverse effects of a drug.

Safety tests	
Type of test	**Approach and goals**
Acute toxicity	• Usually 2 species, 2 routes • Determines therapeutic window (no-effect dose and maximum tolerated dose) and the median lethal dose (LD_{50})
Subacute/ subchronic toxicity	• 3 doses, 2 species • The longer the duration of expected clinical use, the longer the subacute test • Determines biochemical and physiologic effects.
Chronic toxicity	• Rodent (من القوارض كالفأر) and at least one non-rodent species for 6 months • This test is done when the drug is intended to be used for prolonged periods in humans. • Determines biochemical and physiologic effects (same as subacute toxicity test)
Effect on reproductive performance	• 2 species, usually one rodent and at least one rabbit • Testing the effects on animals reproductive performance
Carcinogenic potential	• 2 species, 2 years • This test is done when the drug is intended to be used for prolonged periods in humans • Determines gross and histological pathology
Mutagenic potential	• Testing effects on genetic stability and mutations in bacteria (Ames test) or mammalian cells in culture; dominant lethal test and clastogenicity in mice.

  - **What are the limitations of pre-clinical testing?**
    - ✓ It is time-consuming (might need 2-6 years for data collection and analysis) and expensive.
    - ✓ Large number of animals may be needed.
    - ✓ Extrapolation to humans is reasonably predictive.
    - ✓ Rare adverse effects are unlikely to be detected in pre-clinical testing.

- **IND (Investigational New Drug):**
  - After completing the pre-clinical evaluation in animals, and before testing the new drug in human subjects, sponsors must file an IND (Investigational New Drug) application by which they get a permission from Food and Drug Administration in Unites state to administer the drug to humans.
  - **The IND includes the following information:**
    - ✓ Composition and source of the drug.
    - ✓ Chemical and manufacturing information.
    - ✓ All data from animal studies.
    - ✓ Proposed plans for clinical trials.
    - ✓ Names and credentials (شهادات) of people who will conduct the clinical trials.
    - ✓ A compilation of the key data relevant to study of the drug in humans that has been made available to investigators and their institutional review boards.
  - **The FDA will consume 30 days to review the application. Then, they will response by:**
    - ✓ Approving or disapproving.
    - ✓ Asking for more data.
    - ✓ Allowing initial clinical testing to proceed.
- **Clinical trials:**

Characteristics of different phases			
Phase-I	**Phase-II**	**Phase-III**	**Phase-IV**
First in humans	First in patients	Multi-site trials	Post-marketing surveillance
10-100 participants	50-500 participants	A few hundred to a few thousand participants	Many thousands of participants
Usually healthy volunteers	Patient-subjects receiving the experimental drug	Patient-subjects receiving the experimental drug	Patients in treatment with approved drug
Open label	Randomized and controlled (can be placebo-controlled); may be blinded	Randomized and controlled (can be placebo-controlled); may be blinded	Open label
Safety and tolerability pharmacokinetics	Efficacy and dose ranging	Confirm efficacy in large population	Adverse events, compliance, drug-drug interactions
Months – 1 year	1-2 years	3-5 years	No fixed duration
Success rate: 50%	Success rate: 30%	Success rate: 25-50%	-

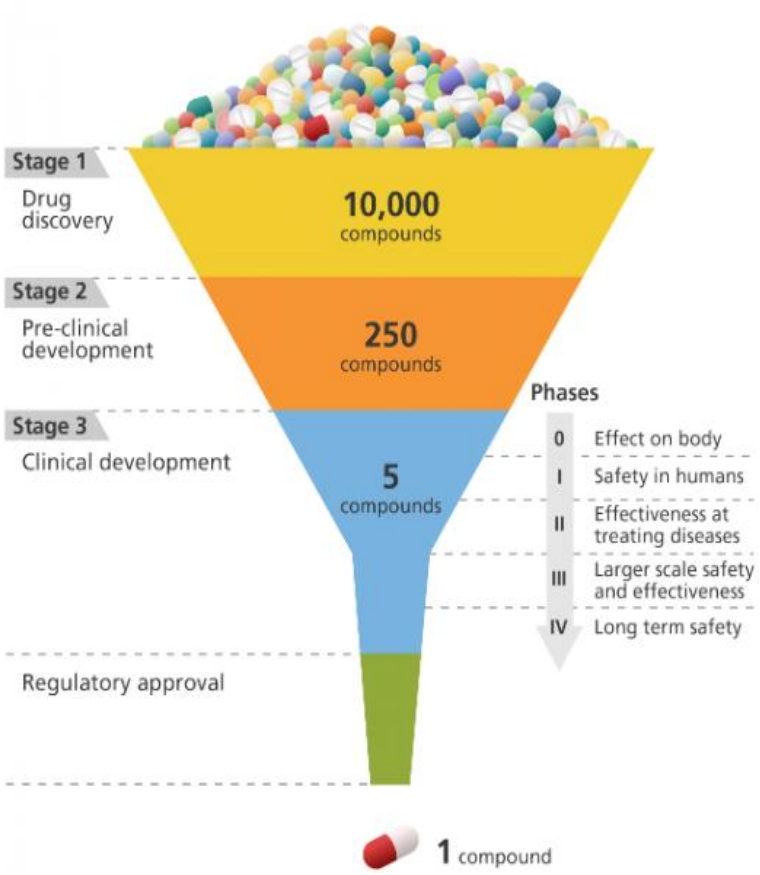
- **Trial methodology (المناهج المُتَّبعة في إجراء التجارب):**
  - ✓ **Randomized**: a type of scientific expirement where the people being studied are randomly allocated one or other of the different treatments under study.
  - ✓ **Controlled**: it is a study testing a specific drug involving two groups of patients with the same disease (one is an experimental group and the other is a control group).
  - ✓ **Parallel**: type of clinical study where two groups of treatments, A and B, are given so that one group receives only A while another group receives only B.
  - ✓ **Crossover**: it is a longitudinal study in which subjects receive a sequence of different treatments (or exposures).
  - ✓ **Open-label**: a clinical trial in which both the researchers and participants know which treatment is being administered.
  - ✓ **Single-blind**: describes experiments where information that could introduce bias or otherwise skew the result is withheld from the participants, but the experimenter will be in full possession of the facts.
  - ✓ **Double-blind**: neither the participants nor the researchers know which participants belong to the control group, nor the test group.

- **NDA (New Drug Application):**
  - If phase-III results meet expectations, sponsors apply to FDA requesting approval to market/ sell the drug.
  - This application will reviewed –from months to years- by specialists from FDA or external experts. Notice that priority approvals (within 6 months) will be given for products which represent significant improvements.
  - The company which produced the drug and the FDA must agree on the (package insert = the official prescribing information) which describes:
    - ✓ Approved indications for using the drug.
    - ✓ Clinical pharmacological information: dosage, adverse reactions. Warnings and precautions (contraindications).

      Notes:
      - ❖ Drug labeling is a summary for safe and effective use of the drug. It must be informative, accurate, not misleading and –when possible- based on data derived from human experience.
      - ❖ Black box warning:
        - ➢ It signifies that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects (which means that the drug can be fatal or causing permanent disability).
        - ➢ By proper use of the drug, a serious adverse effect can be: prevented, reduced in frequency or reduced in severity.
        - ➢ Examples:

Drug	Adverse reaction
All antidepressants	Suicidal tendencies
Rosiglitazone	Heart failure and heart attacks
Celecoxib	CVS and GI diseases
Fluoroquinolones	Tendon rupture and tendinitis
Warfarin	Bleeding to death

- **Post-marketing surveillance:**
  - **It includes the following components:**
    - ✓ Marketing and promotion: the business of advertising or otherwise promoting the sale of drugs.
    - ✓ Prescription:
      - ❖ Many patients.
      - ❖ Multiple diseases.
      - ❖ Multiple drugs.
    - ✓ Monitoring: measuring of medication concentrations in the blood. The main focus is on drugs with a narrow therapeutic range (drugs that can easily be under or overdosed.
    - ✓ Reporting adverse effects of drugs.



- **Meta analysis:**
  - It is a method which focuses on combining results from different studies

- It identifies patterns among study results, sources of disagreement among those results or other interesting relationships that may come to light.
- The general aim of meta analysis is to more powerfully estimate the true effect size as opposed to a less precise effect size derived in a single study under a single given set of assumptions and conditions.
- **Advantages of meta analysis:**
  - ✓ It is able to control between study-variation.
  - ✓ Includes moderators to explain variation.
  - ✓ Has higher statistical power to detect an effect.
  - ✓ Detects publication bias.
  - ✓ Shows whether the results are more varied than expected.
  - ✓ Deals with information overload: many articles published.
  - ✓ It is a generalization to the population of studies.
  - ✓ It is less influenced by local biases than single studies.
  - ✓ Allows derivation and statistical testing of overall factors and effect-size parameters in related studies.