PHARMACOLOGICAL SCREENING AND STANDARDIZATION

**Screening of drugs:** It means thorough investigations
- measure the pharmacological activity of new or chemically undefined substances
- investigate the function of endogenous mediators
- measure drug toxicity and unwanted effects

The main purposes of screening are to determine whether the new substance are worthy for further attention and to indicate which among them have the most interesting pharmacological properties.

**Types of Screening:**

A. Simple screening
B. Blind screening
C. Programmed screening

A- Simple Screening:
It involves the use of one or two simple tests to find substances having a particular property. For example, a single test for conc. of glucose in blood can be used to screen compound for hypoglycemic activity.

B- Blind Screening:
It is used to detect the pharmacological activities of new drugs whose pharmacological activity is unknown. The chief purposes is to demonstrate whether these new drugs are worthy of further attention or not.

C- Programmed Screening:
It is used when a new drug of specific type is to be screened for some pharmacological effects. Examples are screening of certain drugs on the CVS, CNS, kidney, blood etc. It includes the use of quantitative assay of the compounds and their comparison with standard drugs that are quite active representative members of their pharmacological class.
It also provides indications of potential side effects.

**Standardization of drug:**

Bioassay plays a key role in pharmacological screening and standardization of drugs.

**Bioassay:** It is defined as the estimation of concentration or potency of a substance (drugs, hormones, vitamins, toxins, and antitoxin) by measurement of the biological response that it produces.
Pharmacological Applications of bioassay:

- Used in determination of drugs potency
- Screenings of new agents isolated from plants, animals or chemical labs and find their field of activities
- Establishment of SAR (structure activity relationship)
- Essential in monitoring environmental pollutants
- Determination of the pharmacological activities of a new drug
- Determine the therapeutic advantage of one drug over another treatments
- Useful in study of new hormonal or other chemically mediated control systems

Principles of Bioassay:

These are the principles of bioassays:

1. The potency of unknown preparations is compared with that of standard product under identical experimental conditions.
2. Active principle should be identical in both the standard and the preparation to be assayed.
3. Assay experiment should be designed in which the effect observed is not the same as the desired therapeutic effect.

Standards: These are internationally accepted samples of drugs recommended by the Expert Committee of the Biological Standardization of W.H.O.

Dose-response: Comparisons are best made on the basis of dose–response curves.

- I. Graded dose response
- II. Quantal dose response

Relative potency estimation:

- Relative potency = \( \frac{\text{Dose standard}}{\text{Dose sample}} \)
- Relative potency = \( \frac{\text{EC50A}}{\text{EC50B}} \)

EC50: The concentration of drug at which % of Emax is termed half of maximal effective concentration, is abbreviated as EC50
Pharmacologic profile:

A variety of biologic assays at the molecular, cellular, organ, system, and whole animal levels are used to define the activity and selectivity of the drug. Studies are performed during drug screening to define the pharmacologic profile of the drug at the molecular, cellular, system, organ, and whole organism levels.

For example, a broad range of tests would be performed on a drug designed to act as an antagonist at alpha-adrenoceptors for the treatment of hypertension. Anti-infective drugs may be tested against a variety of infectious organisms some of which are resistant to standard agents. Hypoglycemic drugs for their ability to lower blood sugar, etc

- Molecular level:

At the molecular level, the compound would be screened for receptor binding affinity to cell membranes respective receptors, other receptors and binding sites on enzymes. If crystal structures of the drug and target are available, structural biology analyses or computer-assisted virtual screening might be done to better understand the drug receptor interaction.

  - For example, studies on liver cytochrome P450 enzymes would be performed to determine whether the drug of interest is likely to be a substrate or inhibitor of these enzymes or to interfere with the metabolism of other drugs.

- Cellular level:

Effects on cell function would be studied to determine whether the drug is an agonist, partial agonist, or antagonist at a receptors. Isolated tissues, especially vascular smooth muscle, would be utilized to characterize the pharmacologic activity and selectivity of the new compound in comparison with reference compounds. Comparison with other drugs would also be undertaken in other in vitro preparations such as gastrointestinal and bronchial smooth muscle.

- Systems/ Organism levels:

Whole animal studies are generally necessary to determine the effect of the drug on organ systems and disease models. Cardiovascular and renal function studies of all new drugs are generally first performed in normal animals.

  - For a candidate antihypertensive drug, animals with hypertension would be treated to see if blood pressure was lowered in a dose-related manner and to characterize other effects of the compound. Evidence would be collected on duration of action and efficacy following oral and parenteral administration. If the agent possessed useful activity, it would be further studied for possible adverse effects on other major organ systems, including the respiratory, gastrointestinal, endocrine, and central nervous systems.
### Pharmacologic profile tests

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<td>Evidence for receptor activity agonism or antagonism</td>
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<td>Isolated tissue</td>
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<td>Coagulation time, clot retraction, prothrombin time</td>
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<td>Mouse, rat</td>
<td>Degree of sedation, muscle relaxation, locomotor activity, stimulation</td>
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After Screening via Bioassay:

These studies might suggest the need for further chemical modification to achieve more desirable pharmacokinetic or pharmacodynamic properties. For example,

- Oral administration studies might show that the drug was poorly absorbed or rapidly metabolized in liver so; modification to improve bioavailability might be indicated.
- If the drug is to be administered long-term, an assessment of tolerance development would be made.
- For drugs related to or having mechanisms of action similar to those known to cause physical dependence, abuse potential would also be studied.

Lead compound:

The desired result of this screening procedure (which may have to be repeated several times with analogs or congeners of the original molecules) is called a lead compound. Lead compound is now a leading candidate for a successful new drug.

Factors affecting Pharmacological response of drugs:

- **Sex:** Difference in drug response among different sex is attributed to difference in the level of metabolizing enzymes
- **Age:** The level of metabolizing enzymes varies with age and some enzymes may be lacked in newly born animal.
- **Diseases:** E.g. hypersensitivity to catecholamine action on CVS is increased in hyperthyroidism.
- **Environmental:** Such as temperature, seasons, nutrition, light and isolation of animal etc. e.g. the convulsive action of insulin in mice is greatly influenced by temperature

Criteria of a good biological assay:

*Selectivity:* It is ability of the test drug to selectively use a certain signal transduction pathway to act on the same receptor (e.g., histamine selectively acts on histaminic receptors and not muscarinic receptors).

*Sensitivity:* It is the ability of the animal or tissue used in the bioassay to respond to small amounts of the test drug (e.g., in the assay of histamine, the guinea pig ileum is used rather than the rabbit intestine due to the presence of high amounts of histaminase enzyme in the rabbit intestine that catalyze the inactivation of histamine).

*Accuracy:* It is the degree of closeness of measurements of a quantity to its true value.

*Precision:* It is the degree to which repeated measurements under unchanged conditions show the same results.
**Screening of disease:**

The search for unrecognized disease or defect by means of rapidly applied tests, examinations or other procedure in apparently healthy individuals. Screening is testing for infection or disease in population or in individuals who are not seeking health care facilities.

**Types of Screening:**

There are 3 types of screening.

  a) Mass screening
  b) High risk or selective screening
  c) Multiphasic screening

**Mass Screening:**
It means screening of whole population or a subgroup, as for example all adults. It is offered to all, irrespective of the particular risk individual. E.g. tuberculosis, AIDS, hypertension, diabetes, leukemias etc

**High risk or selective Screening:**
Screening will be most productive if applied selectively to high-risk groups. The groups defined on the basis of epidemiological research. E.g. cervix cancer tends to occur relatively less often in the upper social groups as compare to lower social groups etc

**Multiphasic Screening:**
It is defined as the application of two or more screening tests in combination to a large number of people at one time than to carry out separate screening tests for single diseases.

Procedure may include
Questionnaire, clinical examination and a wide range of measurements and investigations include chemical and hematological tests on blood, urine specimen, lung function assessments, audio and visual tests with appropriate staffing organization and specialized equipments.

**Ref:**
- PHARMACOLOGY by H. P. Rang, M. Dale - 5th Ed.
- BASIC & CLINICAL PHARMACOLOGY by ketzung - 10th Ed. (2007)

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THANKS 😊