TOXICOLOGY

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- **Deal with adverse or undesired effects of drugs.**
- **Initial toxicology studies are conducted on rodents.**
- **Another animal: Dog is added.**

The toxicology profile

- **Acute** or short-term toxicity.
- **subacute.**
- **subchronic** toxicity.
- **chronic** toxicity.
- **carcinogenicity** testing.
- **reproduction** studies.
- mutagenicity screening.

Acute or Short-Term Toxicity Studies

- Designed to determine the toxic effects of a test compound when administered in a single dose and/**or in multiple doses over a short period**, usually a **single** day.

- Animals compared with **controls** for **eating** and **drinking** habits, **weight change**, **toxic effects**, **psychomotor** changes, and any other signs over **30** day post dose period.
- **Feces and urine specimens** are collected and clinical laboratory **tests** performed to detect changes in clinical chemistry and other changes that could indicate toxicity.
- unwanted effects, for 30-day post dose period. Feces and urine specimens collected and laboratory tests performed to detect changes

- Animal deaths are recorded

Subacute or Subchronic Studies

- Animal toxicity studies of **3 doses daily for 2 weeks to 2 animal species** are required.
- The initial human dose is 1/10 of highest nontoxic dose (in mg/ kg of subject's weight) shown during animal studies.

Chronic testing

- Drugs given to **humans** for **week** or more, animal studies of **90 to 180** days.
- animal studies for **1 year**. Some animal toxicity studies last **2 years** or longer.

Carcinogenicity Studies

- Carried out in **limited number** of **rat and mouse** strains when there is information on spontaneous **tumor** incidence.
- done with **female and male animals** using high, intermediate, and low doses over a **90** day.

- Carcinogenicity studies are long term **(18 to 24 months**), with surviving animals killed and studied at defined **weeks** during the test period.
- animal death (other than killing).
- tumor incidence
- **Any preneoplastic** lesions

Reproduction Studies

- Any effect of drug on **mammalian reproduction**.
- **Embryonic, prenatal, and postnatal** development.
- Multigenerational effects; and teratology.
- Reproductive studies, on **rat.**
- In **embryo toxicity rabbit** is studied in addition to **rat**.

Genotoxicity or Mutagenicity Studies

- performed to determine effect on **gene, mutation or cause chromosome or DNA damage.**
- Strains of Salmonella typhimurium are routinely used in assays to detect mutations.

Preformulation studies

- solubility, partition coefficient, dissolution rate, physical form, and stability.

Drug Solubility

- A drug administered by any route must possess **aqueous solubility** for systemic absorption and therapeutic response.
- Poorly soluble compounds have incomplete, absorption thus produce minimal response.

- Increase aqueous solubility by:

1. prepare more soluble derivatives of parent compound, such as **salts** or **esters**, by **chemical complexation**,
2. by **reducing particle size**.

Partition Coefficient

- To produce a pharmacologic response, a drug molecule must cross biologic membrane of protein and lipid, which acts as **lipophilic barrier** to many drugs.
- The ability of a drug to penetrate this barrier based on lipids solubility(lipophilic) versus aqueous phase **(hydrophilic).** Partition coefficient is measure of distribution in **lipophilic-hydrophilic** phase system and indicates its ability to penetrate biologic multiphase systems.

Dissolution Rate

- The speed a drug substance dissolves in medium called its dissolution rate.
- dissolution constant, and partition coefficient, can provide indication of drug's absorption potential.
- For a chemical entity, its acid, base, or salt forms, as well as its physical form (e.g., particle size), may result in differences in dissolution rate.

Physical Form

- **The crystal or amorphous** forms and/or the particle size of a powdered drug can affect the dissolution rate, thus the rate and extent of absorption, for a number of drugs.
- **Reducing particle size increase surface** area of poorly soluble drug its dissolution rate in the gut is enhanced.

Stability

- Chemical and physical stability of drug alone, and when combined with formulation components, is critical to preparing a successful pharmaceutical product.
- For drugs susceptible to **oxidative** decomposition, the addition of **antioxidant** stabilizing agents to the formulation may be required to protect the potency.

- Drugs destroyed by **hydrolysis, protection against moisture** in formulation, processing, and packaging may be required to prevent decomposition.
- In every case, drug **stability testing at various temperatures, conditions of relative humidity** (RH)—as 40°C 75% RH/30°C 60% RH—durations, and environments of **light**, **air**, and **packaging** is essential in assessing drug and drug product stability. Such information is vital in developing **label instructions for use and storage**, assigning product **expiration** dating, and packaging and shipping.

- **During Phase 1 studies**: oral drugs capsules are employed containing **active ingredient alone**.
- **Excipients** included in the formulation for Phase 2 trials.
- studies **drug's ADME** undertaken
- During Phase 2, the **final dosage form** is selected and developed for **Phase 3** trials; this is the formulation that is submitted to the FDA for **marketing approval**.

Drug effect in a population sample.

- Certain drugs may produce more than one effect, depending on dose. For example, **a low dose of barbiturate produces sedation, whereas a larger dose produces hypnotic effects.**
- **Age:** newborns and those born prematurely, have immature hepatic and renal function, the means by which drugs are normally inactivated and eliminated from the body.

- **Age or weight is not enough in determine pediatric dose**.
- Many pediatric doses based on **body weight or body surface area** (BSA).
- **Elderly persons:** physiologic functions decrease after 30 years. cardiac output decrease 1%/year from age 20 to 80.
- GFR falls progressively until age 80; at time it is only **half of what it was at age 20**.
- Vital capacity, immune capacity, and liver enzyme function also decrease. The decrease in renal and hepatic function in elderly slows drug clearance rate

Accumulation and toxicity

- **Chronic disorders in old patients require concomitant drug therapy**, increasing

1. drug-drug interactions and
2. adverse effects.

- **Pharmacogenetics** varying effects among different racial populations.
- **Common genetic polymorphisms**: multiple forms of enzymes governing drug metabolism, affect clearance from blood of many drugs used in large patient populations

Body Weight

- Usual doses for drugs are suitable for **70-kg** (150 lb) individuals.
- The ratio between amount of drug administered and the size of the body influences drug concentration in body fluids. Therefore, drug dosage require adjustment heavy patients.
- Mg (drug) /kg (body weight) basis (e.g., 1 mg/kg).
- Body weight is more dependable than age
- In some instances, pediatric dose based on a combination age and weight (e.g., 6 months to 2 years of age: 3 mg/kg/day).

Body Surface Area

- Some drug doses based on (e.g., 1 mg/M^2 BSA).
- The BSA for child or adult determined using **nomogram**.
- The BSA determined at **intersept** of a **straight line drawn to connect an individual's height and weight**.
- For example, an adult measuring 67 in. in height and weighing 132 lb would have a BSA of approximately 1.7 m^2.

Sex

- **Pharmacokinetic differences between women and men**. important for **narrow therapeutic index**.
- Drugs with narrow therapeutic risk increase to toxic levels or decrease to ineffective levels with minimal dosing changes.
- great caution is advised for use of most drugs during **pregnancy** and in women of childbearing age. Similar caution is applicable to drug use in **nursing mothers** because transfer from mother's milk to an infant is well documented for a variety of drugs.

Pathologic State

- example, if drugs used in presence of **renal impairment**, excessive systemic accumulation occur, risking **toxicity**.
- In such conditions, lower doses are indicated, and **if therapy is prolonged**, **blood levels** should be assessed and the patient **monitored** at regular intervals to ensure the maintenance of nontoxic levels of the drug.

Tolerance

- Tolerance common with **antihistamines and narcotic analgesics**.
- After tolerance, normal response may be regained by suspending the drug's administration for a while.

Concomitant Drug Therapy

- Absorption rapid if stomach and upper part of intestine are empty.
- A dose of drug that is effective when taken before a meal less effective if administered during or after eating.
- Drug-food interactions can affect a drug's absorption.

Dosage Form and Route of Administration

- Varying rates and degrees of absorption occur from drug administration in rectum, GIT, under tongue, via skin, and to other sites.
- **Therefore, for a given drug, different dosage forms and routes of administration** are considered new by the FDA.

DRUG PRODUCT LABELING

- Drug labeling includes not only the labels placed on an immediate container but also the information on

1. the packaging,
2. in package inserts, and
3. in company literature,
4. advertising, and promotional materials.

Label contain:

- Description of the product
- Clinical pharmacology
- Indications and usage
- **Contraindications**
- **Warnings**
- Precautions:
- Adverse reactions
- Drug abuse and dependence
- Overdosage, including signs, symptoms
- Dosage and administration
- How supplied

- FDA REVIEW AND ACTION LETTERS
- **POSTMARKETING REPORTING OF ADVERSE DRUG EXPERIENCE**
- **Annual reports**

- **Failure to make required reports may lead to FDA withdrawal of approval for marketing.**

SUPPLEMENTAL NEW DRUG APPLICATION

- A change in the **method** of synthesis
- Change in the **formulation**
- Use of a **different facility** or contractor to manufacture
- Change in the **container** and **closure system**
- Extension of the **expiration date**
- Any **labeling change**

- **Animal drug applications**
- It allows veterinarians to prescribe extra label uses of approved animal drugs and approved human drugs for animals.
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- **Medical devices**
- FDA has regulatory authority over the manufacture and licensing of all medical devices, from **surgical gloves** and **catheters** to **cardiac pacemakers** and **cardiopulmonary bypass blood gas monitors**.

Stability testing of new drug substances and products

- Validation of **analytical procedures** .
- **Impurities** in new drug substances
- Impurities in new drug products
- Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals
- Preclinical testing of biotechnology-derived pharmaceuticals
- General considerations for clinical trials
- Studies in support of special populations: geriatrics
- Ethnic factors in the acceptability of foreign data
- Repeated dose-tissue distribution studies
- Dose selection for carcinogenicity studies of pharmaceuticals
- Dose-response information to support drug registration