Toxicological Approach to Drug development:

- A typical non clinical safety program requires a staged approach.
- With the staged approach, non clinical toxicity studies required to support the next clinical phase are conducted and data made available prior to initiation of that clinical phase, the so-called "just in time" approach to drug development.
- For a first dose-in-humans study, the non clinical safety program generally consists of single dose toxicity studies (two species), repeated-dose toxicity studies (one two species: one rodent one non rodent), local tolerance (generally part of the repeated-dose toxicity studies), and genotoxicity (bacterial mutation assay and in vitro chromosomal damage with mammalian cells or in vitro mouse lymphoma assay) studies.
- These studies usually provide sufficient information to allow dose selection for the first Phase 1 study

Two important determinants of toxicity are:

1. Dose
2. Time

There are three time scales:

1. Dynamic
2. Kinetic
3. Frequency of dosing

- All three are thought to play a role in determining the circumstances leading to toxicity.
- The purpose of the toxicity studies in pharmaceutical development is to provide data in animals that can be used to assess the safety of a compound for human use.

Toxicology and pharmaceutical development:

- For pharmaceutical products, safety must be demonstrated

1. Clinically
2. Non clinically

- Non clinically it is accomplished by conducting:

1. Single dose toxicity
2. Repeated dose toxicity
3. Reproduction toxicity
4. Genotoxicity
5. local tolerance studies

- Depending upon the clinical indication and the level of concern carcinogenicity studies may be required.
- Other studies such as safety pharmacology, special toxicity and pharmacokinetics studies ... may be required and/or provide supportive data for risk assessment.

Single dose toxicity study:

- These guidelines deal with the qualitative and quantitative study of toxic phenomena and their occurrence related to time after a single administration of the substance, or combination of substances.
- These studies may give some indication of the ...

likely effects of acute overdosage in man and may be useful for the design of toxicity studies requiring repeated dosing on the relevant animal species.

- The single-dose toxicity tests should be conducted in such a way that signs of acute toxicity are revealed and the mode of death determined. In suitable species a quantitative evaluation of the approximate lethal dose and information on the dose-effect relationship should be made, but a high level of precision is not required.

#Repeated-dose toxicity:

- Repeated dose toxicity testing using oral administration of a test substance in rodents for 28 and 90 days is used to evaluate chronic toxic effects, primarily effects on various organ system, and to establish a no observed effect level (NOEL).

- Depending on the potential route of human

exposure to the substance, similar testing using dermal and inhalation dosing may also be assessed.

- Doses are selected to be sublethal but still cause toxic effects.
- Long-term chronic toxicity studies with a minimum duration of 12 months are sometimes required.

Reproduction toxicity:

- Reproductive toxicity refers to structural and functional alterations that affect reproductive competence (كفاءة) in sexually mature males and females.
- Reproductive toxicity includes effects on male fertility and female fertility, parturition and lactation.

- Male fertility:

Male reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, reduction in sperm count, alterations in sperm

motility or morphology, aberrant (غير عادي) mating behavior, altered ability to mate, alterations in endocrine function, or overall reduction in fertility.

- Female Fertility:

Female reproductive toxicity includes damage to the reproductive organs, alterations in endocrine regulation of gamete maturation and release, aberrant mating behaviour, altered ability to mate, or overall reduction in fertility.

- Diminished fertility in female animals is typically detected by reductions in the fertility index, the number of implantation sites, time to mating, or fecundity.

Genotoxicity:

Germ cell mutagens / genotoxins are substances that cause heritable (passed on to progeny) changes in the genetic material in germ cells, namely spermatocytes or oocytes. The term mutagen refers to a substance that includes transmissible

- A poisonous substance which damage DNA. A genotoxin can cause mutations in DNA (and so be a mutagen), it can trigger cancer (and so be a carcinogen) or it can cause a birth defect (and so be a teratogen).

changes in DNA Structure involving a single gene or a group of genes.

-Genotoxins are a broader category of substances that induce changes to the structure or number of genes via chemical interaction with DNA and/or non-DNA targets.

*Carcinogen: A substance capable of causing cancer in living tissue.

→ the ability or tendency to produce CANCER.

- Carcinogenicity Studies:

It is required for pharmaceuticals intended for continuous use for atleast 6 months and/or there is a cause for concern.

Causes for concern include:

- Evidence of carcinogenicity in the compound class
- Structure activity relationship suggesting carcinogenic risk
- Evidence of pre neoplastic lesions in repeated-dose toxicity studies
- Long-term tissue retension of parent compound and/or metabolites resulting in local tissue reactions.

Doses of carcinogenicity Studies may be based on one of the following:

- Comparison of AUC in animals and man
- Saturation of absorption
- Pharmacodynamics
- Maximum feasible dose
- Maximum tolerated dose
- limit dose

-Thus two of the six criteria require the use of pharmacokinetic data for selection of the high dose for a carcinogenicity study.

- Chronic toxicity studies consist of six months studies in rodents and nine or twelve months toxicity studies in non rodents.

-This is required only when the duration of clinical use of pharmaceutical is greater than three months.

Outline of Typical Safety Program:

- A typical non clinical safety program requires a staged approach.

•With the staged approach, non clinical toxicity studies required to support the next clinical phase are conducted and data made available prior to initiation of that clinical phase, the so-called "just in time" approach to drug development.

•For a first dose-in-humans study, the non clinical safety program generally consists of single dose toxicity studies (two species), repeated dose toxicity studies (one two species: one rodent one non rodent), local tolerance (generally part of the repeated dose toxicity studies), and genotoxicity (bacterial mutation assay and in vitro chromosomal damage with mammalian cells or in vitro mouse lymphoma assay) studies

•These studies usually provide sufficient information to allow dose selection for the first Phase I study.

•As data becomes available from the initial toxicity studies the toxicologists assesses the findings, reassesses the clinical development plan. And prepares for the next toxicity studies.

•These studies involve the conduct of longer-term repeated dose toxicity, reproductive toxicity and in vivo genotoxicity studies.

•The final type of toxicity is the special toxicity study it is conducted when an issue arises and there is a need to better understand.

#Factors in Designing Studies:

•Several factors must be considered when designing toxicity studies.

•These include the use of main study or satellite animals for collection of pharmacokinetic data, the total blood volume that can be extracted from animals during a given period of time, as well as the amount of blood that can be collected at each time point, route of exposure, Sampling time point, number of animals per time point, number of sampling days and bioanalytical support.

Compound libraries:

- If the lead compound is found to be toxic, it is kept in the compound library for future use.
- A compound library is a collection of compounds
- Compound libraries from past project are kept and may be screened for the biological activity you are looking for in a new project.
- New compounds may also be made "in-house" but nowadays specialist chemical companies are often contracted to simply make NCEs for big pharmaceutical companies.
- A disadvantage of synthetic libraries is that often limited.

lead compound in drug discovery is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may still have suboptimal structure that requires modification to fit better to the target.