BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology

Course Code : BM35C7

Unit-V

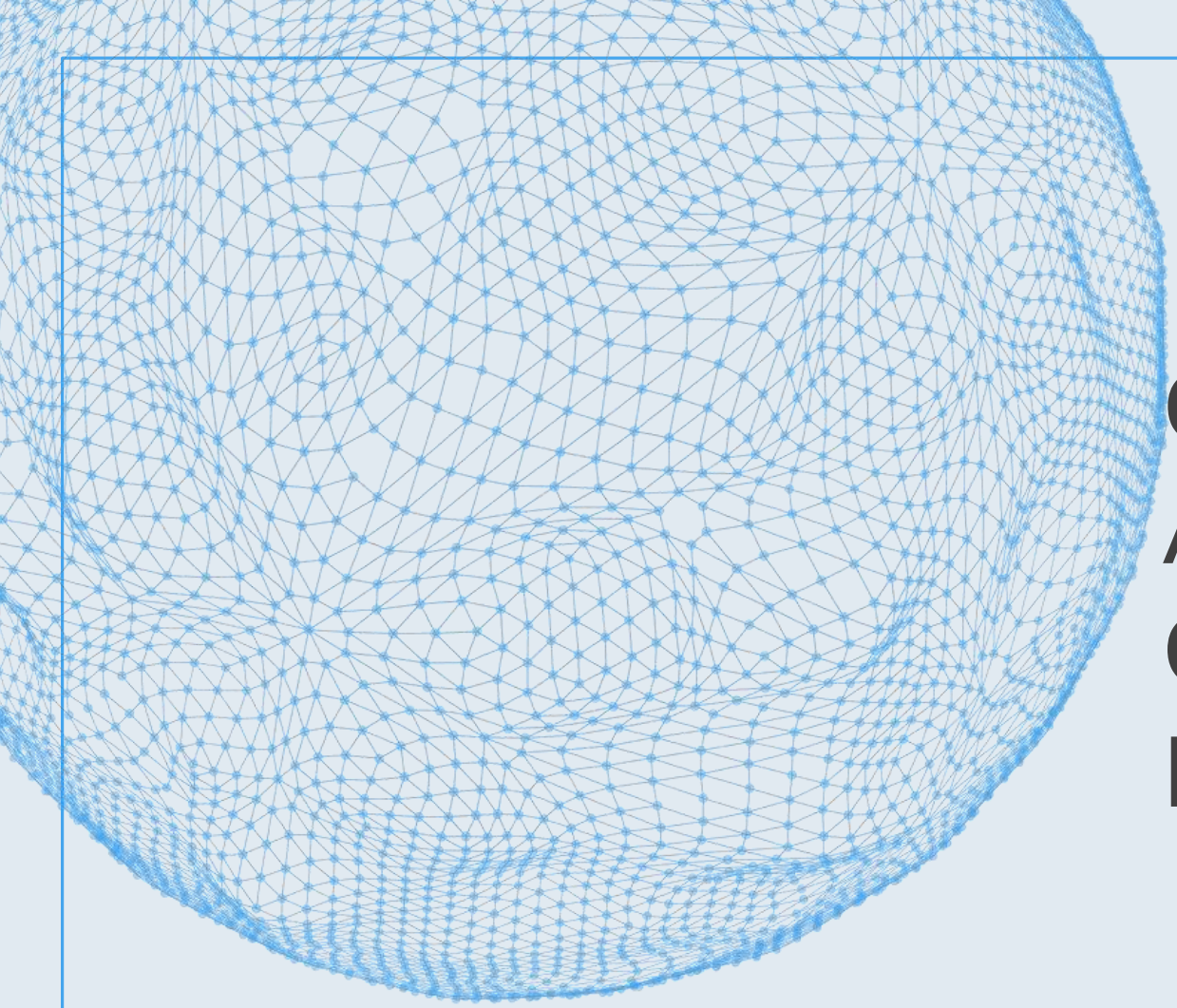
Toxicology- Part 1

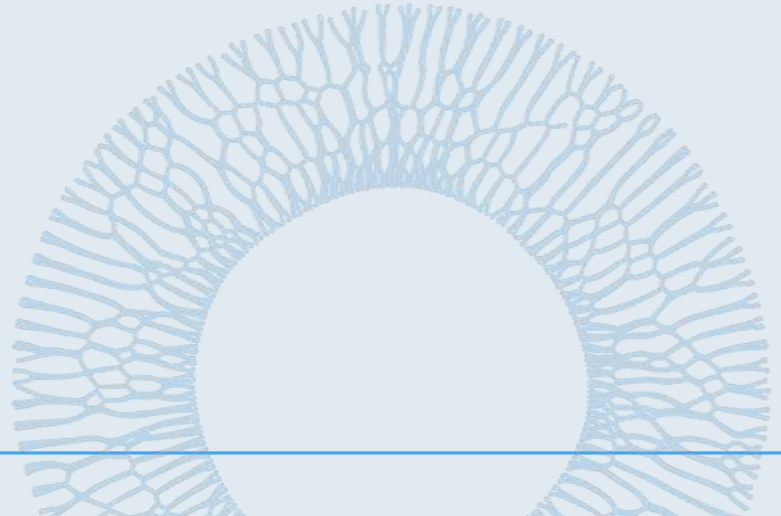
Dr. P.S.Dhivya

Guest Lecturer

Department of Biomedical Science

CHRONIC TOXICITY AND ICH GUIDELINES ON SAFETY PROCEDURES





AGENDA

- Toxicity
- Necessities of toxicological studies
- Types of toxicity studies
- Chronic toxicity studies
- OECD guidelines
- ICH
- Guidelines
- Studies

TOXICITY….???

All substances are poisons, there is none which is not poison. The right dose differenciates a poison from a remedy.(Paracelsus,1493-1541)

Toxicology

It is the study of adverse effects of chemical and physical agents and the degree to which a substance can harm human or animals.

(or)

The study of the nature, effects, and detection of poisons and the treatment of poisoning.

NECESSITIES OF TOXICOLOGICAL STUDIES

- Benefit- risk ratio can be calculated
- Predictions of therapeutic index

$$\text{Therapeutic index} = \frac{\text{Maximum tolerated dose}}{\text{Minimum curative dose}}$$

PRINCIPLE OF TOXICITY STUDIES

- Studies should comply with GLP
- Performed by trained and qualified staff
- Use of standardized and calibrated equipment
- SOP's followed in laboratory tasks.
- All documents should be preserved for minimum 5 years after marketing of the drug.

TYPES OF TOXICITY

ACUTE TOXICITY

- harmful in single or short term exposure.

SUB-CHRONIC TOXICITY

- causes effect by multiple doses or long exposure.

CHRONIC TOXICITY

- Upon repeated dosage or life time exposure.

ACUTE TOXICITY STUDIES

- Repeated dose studies (usually 14 days)- rat,mouse (5-10/sex/dose), dog, monkey (2/sex/dose)
- In-life observation
- Necropsy
- Histopathology
- Clinical pathology (optional)

SUB-ACUTE TOXICITY STUDIES

- 28 day study (3 doses and control)
- Species- rat (10/sex/dose), dog or monkey (2/sex/dose)
- In-life observation
- Clinical pathology
- Necropsy
- Histopathology

SUB-CHRONIC TOXICITY STUDIES

- 13 week study +/- 4 wk recovery (3 doses and control)
- Species- rat (10/sex/dose), dog or monkey (2/sex/dose)
- In-life observations (+/- ophthamology)
- Clinical pathology
- Necropsy
- Histopathology

CHRONIC TOXICITY STUDIES

❖ ***Objectives***

1. Chronic Toxicity Test- To determine the toxicity observing changes in the function, shape, of a living organism.

2. On Reproductive Potential and Future Generations

3. Teratogenicity Test- To determine damage to the birth of the fetus

4. Mutagenicity Test- To test carcinogenicity and genetic impact on the next generation

OECD GUIDELINES FOR TOXICITY STUDIES

❖ Objectives

- Identification of the hazardous properties of a chemist
- Identification of target organs
- Characteristics of the dose –response relationship
- Identification of a no-observed- adverse- effect level (NOAEL)
- Prediction of chronic toxicity effects at human exposure levels.

GENERAL RULES

- ✓ Test animals
- ✓ Management of breeding
- ✓ Test substances
- ✓ Control group
- ✓ Preliminary Tests

PROCEDURE FOLLOWED FOR CHRONIC TOXICITY

Species	Two species recommended, rodent and non rodent (rat and dog)
Age	Young adults
Number of animals	20 of each sex for rodents, 4 of each sex for non rodents per dose level.
Dosage	Three dose levels recommended, includes a toxic dose level and NOAEL, exposures generally for 12 months, FDA requests 24 months for food chemicals.

OBSERVATIONS

- Morbidity or Mortality
- Specific signs of toxicity in particular for neurofunctional and neurobehavioural sign.
- Ophthalmological examination, using an ophthalmoscope or other suitable equipment.
- Body weight
- Haematology and clinical biochemistry:Various blood count level.Eg. Platelet count,etc.

PATHOLOGY

- Study of all body parts i.e internal and external is carried out

- Organ weight, abdominal tissue cavity and their content.

TEST REPORT

Test report should include:-

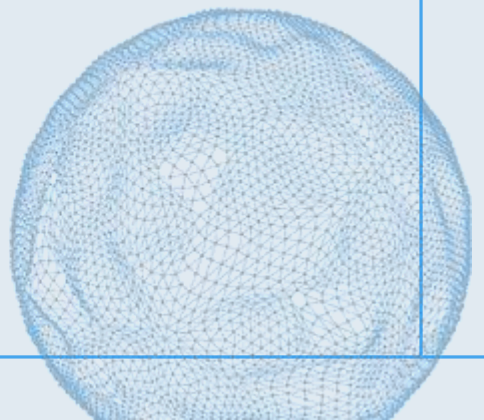
- ❑ Test substance
- ❑ Test animals
- ❑ Test conditions
- ❑ Results
- ❑ Discussions of results including
  - ➢ Dose:response relationships
  - ➢ Consideration of any mode of action information
  - ➢ Discussion of any modelling appoaches

ICH-"INTERNATIONAL COUNCIL FOR HARMONIZATION"

MISSION :-

Unique in bringing together the regulatory authorities and pharmaceutical industries to discuss scientific and technical aspects of drug registration.

Q-Quality Guidelines
S-Safety Guidelines
E-Efficacy Guidelines
M-MultiDisciplinary Guidelines



S1-CARCINOGENICITY STUDIES (S1A-S1C)

S1A-Need for Carcinogenicity Studies of Pharmaceuticals.

- Carcinogenicity Studies are to identify a tumorigenic potential in animals and to access the relevant risk in humans.
- These studies were needed if the clinical use was expected to be continuously for 6 months or longer.
- Whereas, According to the US Food and Drug Administration, Pharmaceuticals generally used for 3 months or more, require this studies.

S1B-TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS

- This document provides the guidance on the need to carry out carcinogenicity studies in both mice and rats.
- This document also provides the guidance that is also given on alternative testing procedures which may be applied without jeopardizing safety.
- This guidelines include the data of mechanistic studies which has cellular changes, biochemical measurements, considerations for additional genotoxicity testing an modified protocols.
- This guideline also helps in the choosing of an appropriate species for long term carcinogenicity testing based on general consideration and also provides the information about the evaluation of carcinogenic potential.

S1C(R2)- DOSE SELECTION FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS

- This document addresses the criteria for the selection of the high dose to be used in carcinogenicity studies on new therapeutic agents to harmonize current practices and improve the design of studies.
- In this revision, pharmacokinetic endpoint of 25 is declared to be applicable also for pharmaceuticals with positive genotoxicity signals.This change has implications on "Refinement" (one of the 3R's) in enhancing the welfare , i.e., reducing the pain or discomfort of the animals at the MTD.
- This guidelines provides data for the conducting of dose-ranging studies, Toxicity endpoints, Maximum feasible dose, limit dose, additional endpoints in high dose selection and selection of middle and low doses in this studies.

S2- GENOTOXICITY STUDIES

S2A-GUIDANCE ON SPECIFIC ASPECTS OF REGULATORY GENOTOXICITY TESTS FOR PHARMACEUTICALS.

- This document provided specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results.It includes a glossary of terms related to genotoxicity tests to improve consistency in applications.

S2B-GENOTOXICITY :A STANDARD BATTERY FOR GENOTOXICITY TESTING FOR PHARMACEUTICALS

- This document addressed two fundamental areas of genotoxicity testing.
- The identification of a standard set of assays to be conducted for registration, and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.
- Registration of pharmaceuticals requires a comprehensive assessment of their genotoic potential. It is clear that no single test is capable of detecting all relevant genotoxic agents. Thereafore the usual approah should carryout a battery of invitro and invivo tests for genotoxicity.

S3-TOXICOKINETICS AND PHARMACOKINETICS (S3A-S3B)

S3A NOTE FOR THE ASSESSMENT OF SYSTEMIC EXPOSURE IN TOXICITY STUDIES

- This document gives guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.
- The primary objective of toxicokinetics is to describe the systematic exposure achieved in animals and its relationship to dose level and the time course of the toxicity study.

S3B- PHARMACOKINETICS GUIDANCE FOR REPEATED DOSE TISSUE DISTRIBUTION STUDIES

- Tissue distribution studies are essential in providing information on distribution and accumulation of the compound and metabolites, especially in relation to potential sites of action, this information may be useful for designing toxicology and pharmacology studies and for interpreting the results of these experiments.
- This document gives guidance, when the repeated dose tissue distribution studies should be considered.It also gives recommendations on the conduct of such studies.

S4-TOXICITY GUIDELINES

S4 DURATION OF CHRONIC TOXICITY TESTING IN ANIMALS (RODENT AND NON RODENT TOXICITY TESTING)

- The objective of this guidance is to set out the considerations that apply to chronic toxicity testing in rodents and non rodents as part of the safety evaluation of a medicinal product.

1. Rodents (a study of 6 months duration)
2. Non-rodents (a study of nine months duration)

S5 REPRODUCTIVE TOXICOLOGY

S5(R2) DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY

- This document provides guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

S5(R3) REVISION OF S5 GUIDELINE ON DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY

Since the adoption of the S5(R2) Guideline experience has been gained with the testing of pharmaceuticals using the current and novel testing paradigms.Additionally, scientific, technological and regulatory knowledge has evolved significantly.Consequently, there are now opportunities for modernising testing paradigms to enhance human risk assessment, while also potentially reducing animal use.There are also areas where the guidance could be revised or amended for greater clarity as well as to align more fully with other more recent ICH Guidelines, such as ICH M3(R2),ICH S6(R1) as well as ICH S9.

S6 BIOTECNOLOGICAL PRODUCTS

S6(R1) PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS

This document covers the pre-clinical safety testing requirements for biotechnological products. It adresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies.

S7A-S7B PHARMACOLOGY STUDIES

S7A SAFETY PHARMACOLOGY STUDIES FOR HUMAN PHARMACEUTICALS

This document addresses the definition, objective and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of phase 1 clinical studies as well as information needed for marketing.

S7BTHE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS

- This Guideline describes a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization.
- This Guideline includes information concerning non-clinical assays and integrated risk assessments.

S8 IMMUNOTOXICOLOGY STUDIES

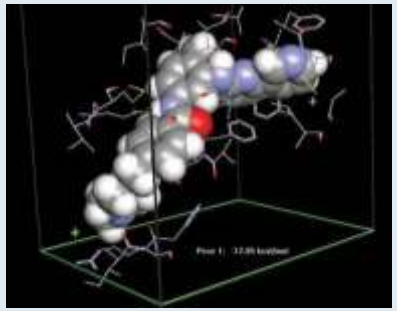
S8 IMMUNOTOXICITY STUDIES FOR HUMAN PHARMACEUTICALS

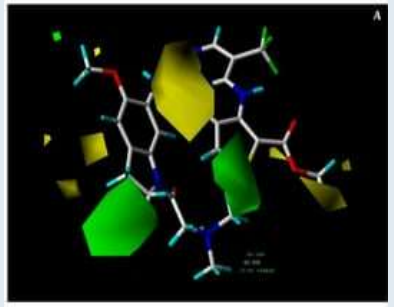
This Guideline addresses the recommendation on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biological).It applies to new pharmaceuticals intended for use in humans, as well as to marketed drug products proposed for different indications or other variations on the current product label in which the change could result in unaddressed and relevant toxicologic issues. In addition, the Guideline might also apply, to drugs in which clinical signs of immunosuppression are observed during clinical trials and following approval to market. The term immunotoxicity will primarily refer to immunosuppression, i.e, a state of increased susceptibility to infections or the development of tumors.

S9 NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS

S9 NONCLINICAL EVALUATION FOR ANTICANCER PHARMACEUTICALS

This Guideline provides information for pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology derived pharmaceuticals. It describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals and references other guidance as appropriate.





S10 PHOTOSAFETY EVALUATION

S10 PHOTOSAFETY EVALUATION OF PHARMACEUTICALS

This Guideline provides international standards for photosafety assessment and harmonises such assessments supporting human clinical trials and marketing authorizations for pharmaceuticals. It includes factors for initiation of and triggers for additional photosafety assessment and should be read in conjunction with ICH M3(R2), Section 14 on Photosafety Testing.

S11 NONCLINICAL SAFETY TESTING

S11 NONCLINICAL SAFETY TESTING IN SUPPORT OF DEVELOPMENT OF PAEDIATRIC MEDICINES

The S11 Guideline is proposed to provide direction on the nonclinical safety studies important to support a padiatric development program. It will recommend standards for the conditions under which nonclinical juvenile animal testing is considered informative and necessary to support paediatric clinicl trials and also provide guidance on the design of the studies.A streamlined drug development and higher scientific rigor while minimizing the unnecessary use of animals will be achieved with the implementation of this new harmonised ICH Guideline.

"Pharmaceutical biomedical research is the bridge between laboratory discovery and patient care. It's where the promise of scientific breakthroughs becomes a reality."

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.