The Role of Regulatory Toxicology in Drug Development

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Presentation Outline

- Drug development process & regulatory toxicology
- Types of regulatory toxicology studies supporting drug development
- Safety-related regulatory guidance
Investigational New Drug (IND)

Toxicology testing
- adverse effects
- reversibility
- human starting dose

New Drug Application (NDA)
Types of Toxicology Studies

- **General toxicology**
  - Single- and repeat-dose studies to identify potential toxicity of a drug candidate
  - Study duration and dosing route depend on clinical treatment

- **Safety pharmacology**: to investigate potential adverse effects of a drug candidate on vital organs, *e.g.*, cardiovascular, central nervous, and respiratory systems

- **Genotoxicity**: to assess the potential for induction of genetic mutations or chromosomal damage

- **Reproductive toxicity**: to evaluate drug effects on development of the zygote through the embryo, fetus, and neonate, all the way to maturity

- **Carcinogenicity studies**: long-term rodent studies to evaluate carcinogenic potential of drug candidates

- **Others**: *e.g.*, phototoxicity testing, impurity qualification toxicology studies
Good Laboratory Practice

- GLP was instituted following cases of animal testing fraud
  - Industrial Bio-Test Laboratories (IBT) in 1980s: thousands of false safety tests for chemicals were reported; IBT president and top executives were convicted by a federal jury of fabricating key product safety tests

- Federal regulations; **must** be followed closely in all pivotal toxicology studies used in support of a new drug application

- GLP helps assure regulatory authorities that the data submitted are a true reflection of the study results, and can be relied upon when making risk/safety determinations
GLP Principles

- **Organization and Personnel**
  - Personnel
  - Testing facility management
  - Study director
  - Quality assurance unit

- **Facilities**
  - Animal care facilities
  - Animal supply facilities
  - Facilities for handling test and control articles
  - Laboratory operation areas
  - Specimen and data storage facilities

- **Equipment**
  - Equipment design
  - Maintenance and calibration of equipment

- **Testing Facilities Operation**
  - Standard operating procedures
  - Reagents and solutions
  - Animal care

- **Test and Control Articles**
  - Test and control article characterization and handling

- **Protocol for and Conduct of a Nonclinical Laboratory Study**
  - Study plan
  - Conduct of a study

- **Records and Reports**
  - Reporting of nonclinical laboratory study results
  - Storage and retrieval of records and data
  - Retention of records

- **Disqualification of Testing Facilities**
ICH S guidance: a comprehensive set of safety guidelines to uncover potential risks like organ toxicity, carcinogenicity, genotoxicity, reprotoxicity, etc.

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Conclusions

- Regulatory toxicology provides science-based safety information of drug candidates, and inform regulatory decision-making.

- Ultimate goal: translate animal responses into an understanding of the risk for human subjects.
Thank you