The Role of Regulatory Toxicology in Drug Development

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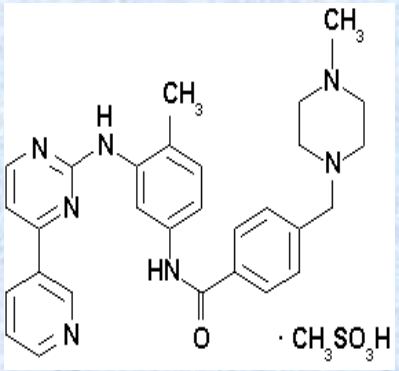
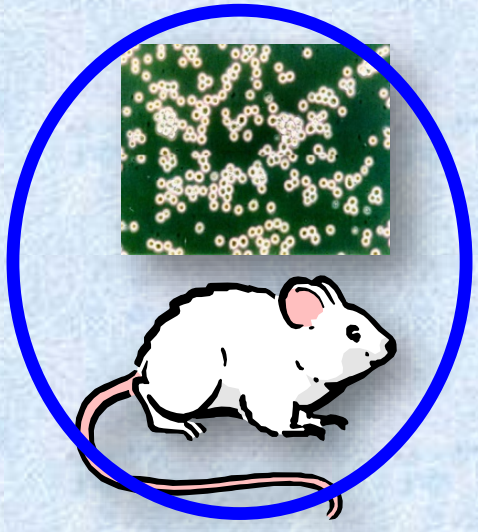
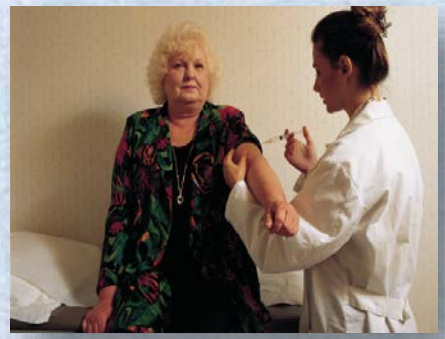
Presentation Outline

- Drug development process & regulatory toxicology
- Types of regulatory toxicology studies supporting drug development
- Safety-related regulatory guidance

Drug Development Process & Toxicology







Toxicology testing
- **adverse effects**
- **reversibility**
- **human starting dose**

Investigational New Drug (IND)

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 Safety Guidelines

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

* ICH: International Council for Harmonization

S1	Carcinogenicity Studies
S2	Genotoxicity Studies
S3	Toxicokinetics and Pharmacokinetics
S4	Chronic Toxicity Testing
S5	Reproductive Toxicology
S6	Nonclinical Evaluation for Biotechnological Products
S7	Safety Pharmacology Studies
S8	Immunotoxicology
S9	Nonclinical Evaluation for Oncology Pharmaceuticals
S10	Photosafety Evaluation
S11	Nonclinical Pediatric Safety
M3	Nonclinical Evaluation for Non-Oncology Pharmaceuticals

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