Pharmacology & Toxicology in the Investigator's Brochure

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Clinical Investigator Training Course – December 11, 2024

Learning Objectives

- Describe the types of nonclinical information provided in the Investigator's Brochure (IB)
  - Pharmacology
  - Safety pharmacology
  - Pharmacokinetics/ADME
  - Toxicology
    - General toxicology
    - Genetic toxicology
    - Other toxicology studies including reproductive toxicology
- Familiarize with references such as International Council for Harmonization (ICH) and/or FDA guidances for Industry.

Nonclinical Information in the IB

- Pharmacology
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Pharmacology

- Proof of Concept
  - Mechanism of action
  - Activity (in vitro and/or in vivo)
- Primary (intended) and secondary (unintended) targets
- Support toxicology species selection
- Type and amount of data varies
  - Product type (e.g., small molecule vs. biologic)
  - Indication (i.e., oncology or non-oncology)
  - Stage of drug development

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Safety Pharmacology

Assess the potential effects on physiological functions on vital organ systems

- Cardiovascular
  - In vitro
  - In vivo (generally non-rodent; dog or monkey)
- Central nervous system (generally rodent)
- Respiratory system (generally rodent)

Studies use the intended clinical route of administration.

ICH S7 Guidance for Industry

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Pharmacokinetics/ADME

- Pharmacokinetics (PK)
  - A drugs' movement through the body
  - Describes parameters e.g., exposure, half-life, clearance
- ADME
  - Absorption (process to systemic exposure)
  - Distribution (drug presence organs/tissues, efficacy/toxicity)
  - Metabolism (pathways of metabolism, species comparison, human unique metabolites)
  - Excretion (mode of elimination of the drug)

Toxicokinetics

- Study of ADME in the general repeat dose toxicology studies (doses may be toxic to animals).
- Informs on parameters such as:
  - Dose proportionality in exposure.
  - Potential saturation in exposure.
  - Sex differences in exposure.
  - Accumulation following repeated dosing.
  - Loss of exposure due to anti-drug antibodies (biologics).

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General Toxicology

Conducted to:

- Determine if the proposed clinical study is reasonably safe.
- Determine a clinical start dose and guide dose escalation for the clinical study.
- Identify potential dose limiting toxicities to inform clinical safety monitoring.
- Assess potential toxicities that cannot be identified in clinical trials.

General Toxicology

Same route of administration and schedule as clinical study in a rodent and non-rodent species.

- Duration of nonclinical studies relative to clinical development described in ICH M3R2 guidance.
  - 2-weeks in two species (rodent, non-rodent) to support a trial up to 2 weeks.
  - Follow the clinical trial timeframe for studies lasting between 2 weeks and 6 months.
  - 6-months (rodent) and 9-months (non-rodent) to support clinical trials lasting longer than 6 months.
- Oncology pharmaceuticals follow ICH S9 and ICH S9 Q&A guidance.
  - 1-month duration to support FIH trials in two species (rodent, non-rodent).
  - 3-month duration to support a registrational trial intended to support a marketing application in two species (rodent, non-rodent).

For biological pharmaceuticals there may only be one species for toxicology studies or none.

General Toxicology

Regulatory guidelines accept data from a variety of species.

Species commonly used

- Rodent – mouse, rat
- Non-rodent – dog, monkey, rabbit

Species selection depends on the drug target and pharmacological relevance.

- Small molecules – may be based on metabolism
- Biologic – generally based on target binding

General Toxicology – Example

- Drug/Indication: Microtubule inhibitor being developed for treatment of advanced solid tumors.
- Produced irreversible optic nerve degeneration at mid and high doses in the rat repeat-dose toxicology study.
- Based on concerns monitoring was increased (optic exams and imaging), and information was added to the protocol and informed consent.

General Toxicology – Example

- Drug class/Indication: Epigenetic targeting drugs being developed for treatment of solid tumors and hematologic malignancies.
- Produced malignancies (lymphoma) in rat 3-month repeat-dose toxicology studies.
- Secondary malignancy has also been observed in clinical trials.
- Based on concerns, patient populations being studied were considered and information was added to the IB and informed consent.

General Toxicology – Example

- Drug class/Indication: antibody drug conjugate with topoisomerase 1 inhibitor payload
- Led to severe kidney toxicity (increased urine protein, proteinaceous casts and multifocal necrosis) in the monkey repeat dose toxicology study.
- Due to observed toxicity especially to kidney, the proposed clinical start dose was lowered from the Sponsor proposed dose and dose escalation was modified.
- Kidney toxicity was observed in the clinical trial leading to additional safety monitoring, update to the IB and the patients informed consent form.

General Toxicology – Example

- Drug class/Indication: immune-agonist developed for patients with urothelial carcinoma to be dosed locally in the bladder.
- Low systemic exposure observed in the monkey repeat dose toxicology study.
- Clinical safety monitoring of up to 6 hours post first dose was added to the protocol due to risk of cytokine release syndrome.

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Genetic Toxicology

- Drugs may be carcinogenic.
- Carcinogenicity study results generally available at the time of drug approval.
  - Not warranted for pharmaceuticals administered infrequently or for short duration of exposure (ICH S1).
  - Not warranted for advanced cancer indications (ICH S9).
- Genetic toxicology studies are:
  - surrogate for carcinogenicity; and
  - help address concerns about risks to humans.
- Results can inform on duration of contraception.

Typical Genetic Toxicology Studies

Genetic toxicology studies are generally conducted with small molecule drugs.

- In vitro
  - A test for gene mutation in bacteria.
  - An assay in mammalian cells to detect chromosomal damage.
- In vivo
  - An assay in rodent species to detect chromosomal damage to hematopoietic cells.

Other genetic toxicology assays may be conducted (ICH S2).

Timing of Genetic Toxicology Studies

Relative to clinical development:

- Gene mutation assay to support a single dose clinical study.
- An additional chromosomal damage study if proposing multiple doses in a clinical study.
- Complete battery conducted prior to Phase 2.
- For oncology pharmaceuticals, studies may be submitted with the marketing application.
  - Results from genetic toxicology studies are warranted for studies conducted in healthy volunteers during drug development.

Nonclinical Information in the IB

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Teratogenicity (e.g. Thalidomide)

- Prescribed to pregnant women for nausea and insomnia in the 1950s and 1960s.
- Resulted in over 10,000 births with severe limb malformations.
- Use in pregnant women banned in 1961.
- Link between exposure and adverse effects was possible because of the potency of the drug and relative short time period between exposure and manifestation of effects.
  - The sensitive period to thalidomide during pregnancy is ~ days 20–34 after fertilization.

Kim and Scialli. *Toxicological Sciences*, Volume 122, Issue 1, July 2011, Pages 1–6

Reproductive Toxicology

- Considerations
  - Patient population (e.g., males, women of childbearing potential, women not of childbearing potential)
  - Small molecule vs biotechnology-derived pharmaceuticals
- Studies that cover fertility, embryo-fetal, and pre- and post-natal periods typically follow M3(R2), S5(R3), S6(R1)
- For oncology indications, also consult ICH S9 and the guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry*

Summary

Nonclinical studies are an important part of drug development to inform on the mechanism of action of the drug, the safety of a proposed first in human clinical dose, the potential toxicities that may be observed during clinical studies and inform on the possible long-term adverse effects during the life cycle of the drug post approval.

Resources

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

- S1 Carcinogenicity Studies
- S2 Genotoxicity Studies
- S3 Toxicokinetics and Pharmacokinetics
- S4 Toxicity Testing
- S5 Reproductive Toxicology
- S6 Biotechnology-derived Products
- S7 Safety Pharmacology Studies
- S8 Immunotoxicology Studies
- S9 Nonclinical Evaluation for Anticancer Pharmaceuticals
- M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials
- Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations

Challenge Question #1

The safety pharmacology core battery does not include:

A. Cardiovascular system

B. Central nervous system

C. Respiratory system

D. Renal system

Challenge Question #2

A complete battery of genotoxicity studies for non-oncology indications should be completed:

A. Prior to the FIH IND stage.

B. Prior to initiating a Phase 2 study.

C. Prior to submitting a registrational clinical trial intended to support drug approval.

D. At the time of the marketing application.

Thank you