

Pharmacology & Toxicology Information to Support Early Drug Development

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Learning Objectives

- Search for additional information in FDA guidance documents
- Describe the types of nonclinical information in the Investigator's Brochure (IB)
 - Pharmacology
 - Safety pharmacology
 - Toxicology
 - General toxicology
 - Genetic toxicology
 - Other toxicology studies: reproductive toxicology

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

Investigational New Drug Application

- **§312.55 Informing investigators.**
 - (a) Before the investigation begins, a sponsor (other than a sponsor-investigator) shall give each participating clinical investigator an investigator brochure containing the information described in §312.23(a)(5).

- **§312.23 IND content and format.**
 - (a)(5) *Investigator's brochure.*
 - ...
 - (ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
 - ...

Nonclinical Information in the IB

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Pharmacology

- Mechanism of action
- Activity (in vitro and/or in vivo)
- Primary (intended) and secondary (unintended) targets
- Type and amount of data can vary
 - Product type (e.g., small molecule vs. biologic)
 - Indication (i.e., population)
 - Stage of development

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Safety pharmacology

Studies to investigate potential for effects on physiological functions

- Cardiovascular
- Central nervous system
- Respiratory

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General toxicology

- Determine whether proposed clinical investigation is reasonably safe
- Determine an initial dose for clinical study
- Identify potential dose limiting toxicities and inform clinical monitoring
- Assess potential toxicities that cannot be identified in clinical trials

Toxicology in the IB: Example

- Biologic/Indication: antibody-drug conjugate being developed for treatment of cancer
- Findings in animals included myelosuppression and severe hepatotoxicity (necrosis, increased liver enzymes)
- How much to worry about hepatotoxicity?

General toxicology

- Design considers planned clinical study
 - Route of administration
 - Schedule of administration
- Relevance of nonclinical species
 - pharmacologically relevance
- Nonclinical data inform the investigator and the patient

Toxicology in the IB: Example

- Drug/Indication: microtubule inhibitor being developed for treatment of advanced solid tumors
- Produced irreversible optic nerve degeneration at mid and high doses in rat repeat-dose toxicology study
- Monitoring was increased (optic exams and imaging) and information was added to the IB and informed consent

Toxicology in the IB: Example

- Drug/Indication: epigenetic targeting drug being developed for treatment of solid tumors and hematologic malignancies
- Produced malignancies (lymphoma) in rat 3-month repeat-dose toxicology studies
- Secondary malignancies observed in clinic
- Considering patient population, information was added to the IB and informed consent

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Genetic toxicology

- Results from carcinogenicity studies are generally not available until the time of product approval
- Genetic toxicology studies
 - used as a surrogate for carcinogenicity
 - help address concerns about risks to human subjects during clinical studies

Typical genetic toxicology studies

- A test for gene mutation in bacteria.
- An in vitro cytogenetic test for chromosomal damage in mammalian cells.
- An in vivo test for genotoxicity, generally a test for chromosomal damage using rodent hematopoietic cells.

Timeline for genetic toxicology

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 anticancer drugs, the battery may be submitted with the marketing application

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Reproductive toxicology example:

Thalidomide-induced birth defects



- Thalidomide prescribed during pregnancy for nausea and insomnia; over 10,000 births with severe limb malformations
- Potent and relatively short time period between exposure and adverse effects
- Nonclinical data can provide information on potential reproductive toxicities in humans

Reproductive toxicology

- Considerations
 - Influence of patient population
 - Small molecule (standard protocols) vs. biotechnology-derived pharmaceuticals (more case-by-case)
- 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 S9 and the guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations Guidance for Industry*

Wrap-up

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Challenge Question #1

What FDA guidance is most relevant for nonclinical drug development in oncology?

- A. M3(R2)
- B. S1B
- C. M7
- D. S9

Challenge Question #2



The safety pharmacology core battery includes:

- A. Cardiovascular system
- B. Central nervous system
- C. Respiratory system
- D. All the above



Thank You



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