# 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

# 21 CFR 312
# 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

- Pharmacology
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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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