

# Pharmacology/Toxicology in the Investigator's Brochure

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# Objectives

- Identify regulations related to pharmacology/toxicology information in the Investigator's Brochure (IB)
- Describe the types of nonclinical information in the IB
  - Pharmacology
  - Safety Pharmacology
  - Toxicology
    - General toxicology
    - Genetic toxicology
    - Other toxicology studies: Reproductive toxicity
- Discuss examples of nonclinical data in the IB



# 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.* If required under §312.55, a copy of the investigator's brochure, containing the following information:
    - (ii) A summary of the pharmacological and toxicological effects of the drug in animals and, to the extent known, in humans.
    - (iii) A summary of the pharmacokinetics and biological disposition of the drug in animals and, if known, in humans.
- **§312.53 Selecting investigators and monitors.**
  - (f) Has read and understands the information in the investigator's brochure, including the potential risks and side effects of the drug
- **§312.42 Clinical holds and requests for modification.**
  - (b)(iii) The investigator brochure is misleading, erroneous, or materially incomplete

# Nonclinical information included in the IB



- Pharmacology
- Safety Pharmacology
- Toxicology
  - General toxicology
  - Genetic toxicology
  - Other toxicology studies

# Pharmacology

- Used to define intended and unintended targets and/or effects
- Amount of information varies
  - Type of molecule (e.g. small molecule vs biologic)
  - Stage of drug development
  - Indication

# How much attention to pay to the pharmacology?

- Drug not the first in class? Better idea of toxicities
- For biologics (e.g. an antibody): Which species best predicts toxicities in humans?
- Can explain some toxicities seen in animals: Exaggerated pharmacologic effects

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# Safety pharmacology

- Cardiovascular
  - In vitro
  - In animals (dogs or monkeys)
- CNS (usually rodents)
- Respiratory (usually rodents)



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# General toxicology

- Toxicology studies with the same route and schedule of administration as proposed in subjects:
  - Duration of nonclinical studies relative to clinical development described in the International Council for Harmonisation (ICH) guidance M3(R2)
  - Anticancer pharmaceuticals follow ICH S9

# Purpose of these studies

- Determine whether conduct of the proposed clinical investigation is reasonably safe
- Determine an initial dose for clinical trials
- Help determine a stopping dose (if necessary)
- Identify potential dose limiting toxicities and inform clinical monitoring
- Assess potential toxicities that cannot be identified in clinical trials

# Species commonly used

- Rodents
  - Rats
  - Mice
- Non Rodents
  - Beagle dogs
  - Cynomolgus monkeys
  - Rabbits

Species typically chosen based on availability of historical control data and pharmacological relevance

# Toxicology studies for biologics

- Species should be pharmacologically relevant
- Safety evaluation normally includes two relevant species
- One relevant species may be sufficient if only one relevant species is identified or the biological activity is well understood

# Toxicity information in the IB: Real examples

- Drug/Indication: Humanized IgG1 monoclonal antibody being developed for treatment of systemic amyloidosis
- Target (amyloid fibrils) not present in healthy animals (pivotal toxicology studies are conducted in healthy animals)
- How is toxicity assessed in the absence of a relevant species? What to monitor in patients?

# Toxicity information in the IB: Real examples

- 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 protocol and informed consent

# Toxicity information in the IB: Real examples



- Drug/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 a clinical trial with one drug
- Considering patient population, information was added to the IB and informed consent



# Toxicity information in the IB: Real examples

- Drug/Indication: Antibody-drug conjugate being developed for treatment of cancer
- Cynomolgus monkey was relevant species
- Findings in monkeys: Myelosuppression
- Findings in rats: Myelosuppression, severe hepatotoxicity (necrosis, increased liver enzymes)
- How much to worry about hepatotoxicity?

# Toxicity information in the IB: Real examples



- Drug/Indication: Fusion protein to inhibit the complement pathway being developed for treatment of paroxysmal nocturnal hemoglobinuria (PNH)
- 100% homology to human protein sequence
- 60% homology to protein sequences in rat
- 90% homology to protein sequences in cynomolgus monkeys
- Deaths in rats and monkeys, due to immunogenicity
- Is immunogenicity relevant to humans?

# General toxicology used to define the starting dose in humans

## Should I worry about the starting dose?

- The FDA reviewed the nonclinical data in the investigational new drug application (IND) and agreed on the starting dose
- Be aware of toxicities
- Understand what the nonclinical data mean and how relevant they are

# **In general, animals are good predictors of toxicities in humans**

- Signal transduction pathways, e.g. inhibition of growth pathways and hyperglycemia
- Infusion reaction to antisense oligonucleotide in monkeys reduced by slower infusion and lower maximum concentration (C<sub>max</sub>)
- Hematologic toxicities of cytotoxic drugs predicted by animal studies



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# Genetic toxicology

- Concern about human exposures during drug development
- Results from carcinogenicity studies are generally not available until the time of product approval
- Genetic toxicology studies used as a surrogate for carcinogenicity during clinical trials

# Types of genetic toxicology assays

- *In vitro*
  - Bacterial assay to detect mutations Ames Test - *Salmonella* and *E.coli*
  - An assay in mammalian cells to detect chromosomal damage
    - Chinese Hamster Ovary (CHO) cells
    - Mouse lymphoma cells
- *In vivo*
  - An assay in a rodent species to detect chromosomal damage to hematopoietic cells
- Other genotoxicity assays are available and may be conducted

# Timeline for genetic toxicology

Relative to clinical development:

- Gene mutation assay for single dose clinical studies
- Add chromosomal damage study if multiple doses in clinical studies
- Complete battery conducted prior to phase 2
- For anticancer drugs, submit with marketing application



# Worried about results of genetic toxicity studies?



- If review team made a decision that the trial is reasonably safe to proceed, either:
  - Negative results in genetic toxicology assays
  - Positive or likely/possibly positive (based on mechanism of action, other drugs in the same class, equivocal results)
    - Life-threatening indication/cancer? Genetic toxicology studies not needed until marketing application; short life-expectancy
    - Serious condition and no other therapy?
    - A single, sub-therapeutic dose in humans?

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# Thalidomide-induced birth defects

- Thalidomide prescribed to pregnant women for nausea and insomnia; over 10,000 births with severe limb malformations
- Potent and relatively short time period between exposure and adverse effects
- Animals can provide information on potential reproductive toxicities in humans
  - Thalidomide-like limb abnormalities in monkeys are induced by thalidomide analogs
  - Hormonal agents (e.g. estrogen receptor agonists) and pregnancy loss

# Development and reproductive toxicology

- Studies that cover fertility, embryo-fetal, and pre- and post-natal periods typically follow ICH 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*
- Considerations
  - Influence of patient population (e.g., women of child bearing potential, pregnant women, etc.)
  - Small molecule (standard protocols) vs. biotechnology derived pharmaceuticals (more case-by-case)

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# Guidelines and Guidances

<https://www.fda.gov/drugs/guidances-drugs/all-guidances-drugs>

- S1 Carcinogenicity Studies
- S2 Genotoxicity Studies
- S3 Toxicokinetics and Pharmacokinetics
- S4 Toxicity Testing
- S5 Reproductive Toxicology
- S6 Biotechnological 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 Guidance for Industry



**Thank You**

# Challenge Question

a) How many ICH topic categories are used for guidelines? b) What categories do M and S stand for? c) List one M guidance and one S guidance relevant to nonclinical information in the IB.





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