FDA's Clinical Investigator Course

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Pharmacology/Toxicology in the Investigator Brochure

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Abbreviations

- **ADME**: absorption, distribution, metabolism, excretion
- **HU**: hydroxyurea
- **IB**: Investigator Brochure
- **ICH**: International Conference on Harmonisation
- **IGFR**: insulin-like growth factor receptor
- **IND**: Investigational New Drug application
- **MOA**: mechanism of action
- **mTOR**: mammalian target of rapamycin
- **PNH**: paroxysmal nocturnal hemoglobinuria

Objectives

- An overview of Pharmacology/Toxicology (nonclinical) information
  - Pharmacology
  - Safety Pharmacology
  - Toxicology
    - General toxicology
    - Genetic toxicology
    - Other toxicology studies: reproductive toxicity
- Examples of toxicity data

Nonclinical information included in the Investigator Brochure (IB)

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

Pharmacology

Pharmacology

- Used to define intended and unintended targets/ 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

Safety Pharmacology

Safety Pharmacology

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

General Toxicology

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 ICH guidance M3R2
  - Anticancer pharmaceuticals follow ICH S9

Purpose of these studies

- Determine whether it is safe to put drug candidate into humans
- Determine an initial safe dose for human clinical trials
- Help determine a safe stopping dose (if necessary)
- Identify dose limiting toxicities (what should be monitored in clinical trials)
- Assess potential toxicities that cannot be identified in clinical trials

Which Species to Test

- Regulatory guidelines accept data from a variety of species
- In practice, only a small number of rodent and nonrodent species are consistently chosen
- Species are chosen because they have been used before, and studied extensively

Species Commonly Used

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

Species in toxicology studies

- For biotech derived products, e.g. an antibody, the species should be pharmacologically relevant. Toxicology studies in a second species may be waived if no other relevant species has been identified.

Toxicity information in the IB: Real examples

- Indication: Treatment of systemic amyloidosis
- Target: amyloid fibrils
- Drug: Humanized IgG1 monoclonal antibody
- Target not present in healthy animals
  (pivotal tox 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

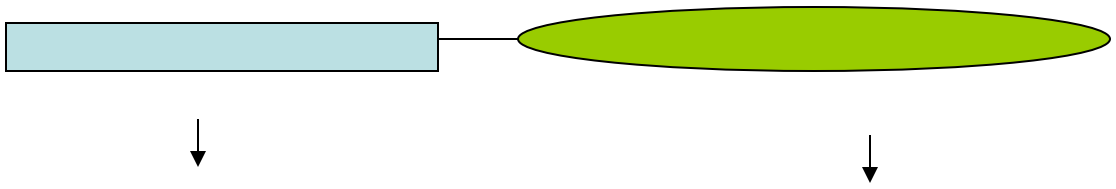
- Drug/Indication: Microtubule inhibitor being developed for treatment of advanced solid tumors
- Produced irreversible optic nerve degeneration at mid and high doses in rat repeat-dose toxicology study
- Based on concerns monitoring was increased (optic exams and imaging), and information was added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

Toxicity information in the IB: Real examples

- Ab-drug conjugate (indication: cancer)
- Cynomolgus monkey was the relevant species
- Findings in monkeys: mainly myelosuppresion
- Findings in rats: myelosuppression, also severe hepatotoxicity (necrosis, increased liver enzymes)
- How much to worry about hepatotoxicity?

Toxicity information in the IB: Real examples

- Fusion protein to inhibit the complement pathway (immune system)
- Indication: PNH



100% homology to human sequences

100% homology to human sequences

Cont'd

- 60% homology to protein sequences in rat
- 90% homology to protein sequences in Cyno
- 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 review team reviewed the IND package and agreed on the starting dose.
- Be aware of toxicities
- Understand what the nonclinical data mean and how relevant they are

… and how relevant are they?

- ADME differences between test animals and humans (*e.g.*, N-acetylation)
- Species differences in anatomy (gall bladder) and physiology (folate levels)
- Species differences in pharmacodynamic responses (binding affinities)

Other limitations

- Adverse reactions that can only be communicated verbally by the patient are not normally recognized in animals (e.g. pain)
- Concomitant drugs in humans may exacerbate toxicity

In general, animals are good predictors of toxicities in humans

- Signal transduction pathways, e.g. IGFR/mTOR inhibition and hyperglycemia
- Infusion reaction in monkeys to antisense oligonucleotide
  - Cmax-related: slower infusion reduces infusion reaction
- Hematologic toxicities of cytotoxic drugs predicted by animal studies

Genetic Toxicology

Genotoxicity

- Data from genotoxicity studies are used as a surrogate for carcinogenicity during clinical trials.
- Results from carcinogenicity studies are generally not available until the time of product approval. Many people, including healthy volunteers, will have been exposed to pharmacologically active doses before carcinogenicity data are available.

Types of genotoxicity assays

- *in vitro*
  - An assay in bacteria to detect mutations in a target gene
    - 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

Timing

- Timing of genetic toxicology studies relative to clinical development
  - Gene mutation assay for single dose clinical studies
  - Add chromosomal damage study for multiple dose clinical studies
  - Complete battery conducted prior to phase 2
  - Submit with marketing application for anticancer drugs

Worried about results of genetic toxicity studies?

- Review team made a decision that the trial is reasonably safe to proceed
  - Negative results in genotoxic assays
  - Positive or likely/possibly to be positive (based on MOA, other drugs in the same class, equivocal results)
    - Life-threatening indication/ cancer? Genotox studies not needed until marketing application; short life-expectancy
    - Serious condition and no other therapy? HU in sickle cell
    - A single, small/sub-therapeutic dose in humans?

A few typical daily exposures to carcinogens

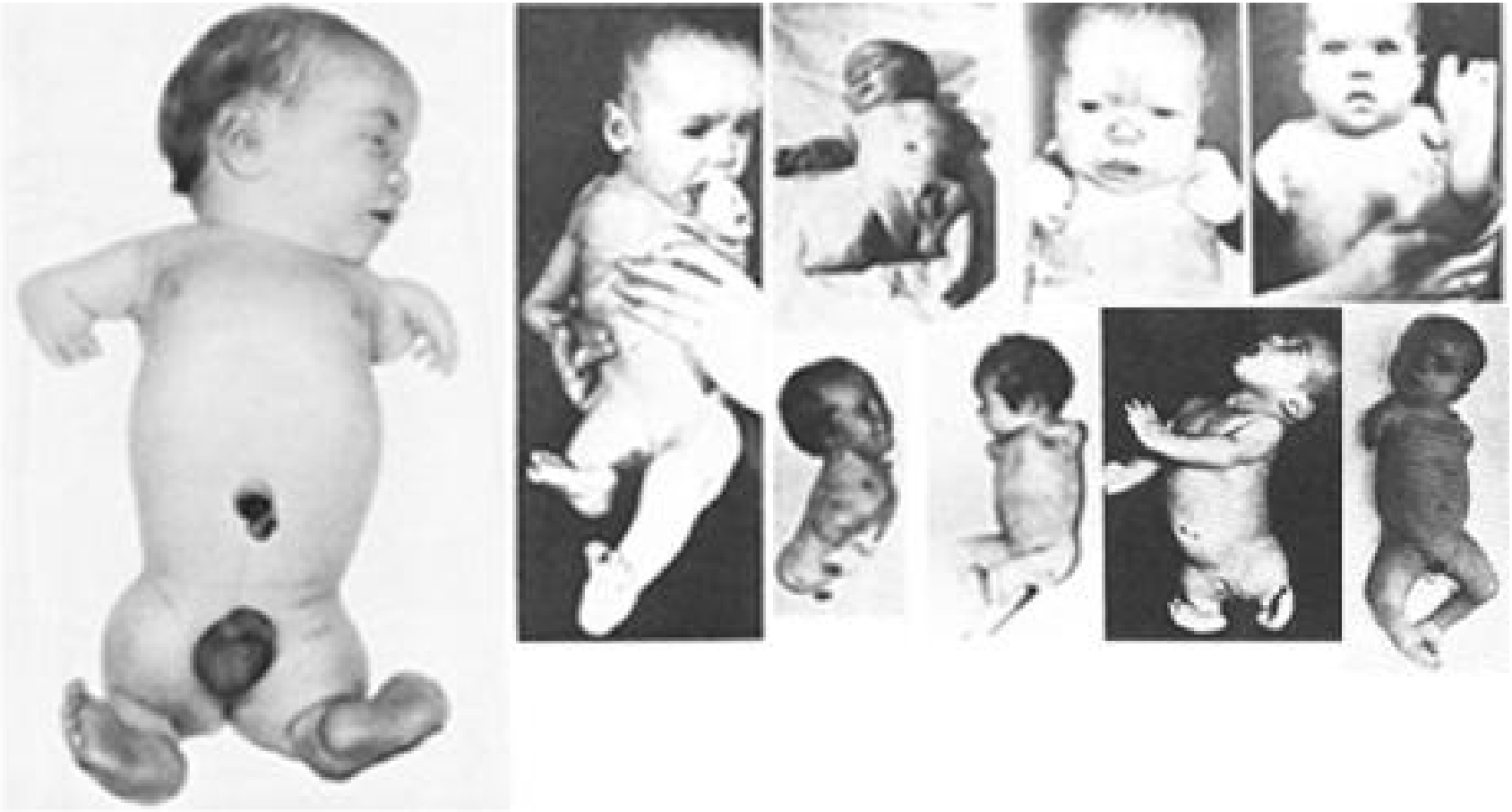
Source of carcinogen	Carcinogen	Average daily human exposure
Indoor air	Formaldehyde Benzene	598 µg 155 µg
Tap water	Bromodichloro-methane chloroform	13 µg 17 µg
Celery	8-methoxy psoralen	4.9 µg
Coffee	Catechol Hydroquinone Caffeic acid	1.3 mg 333 µg 23.9 mg
Lettuce	Caffeic acid	7.9 mg
Brown mustard	Allyl isothiocyanate	62.9 µg

Other toxicity studies: Reproductive toxicology

Teratogenicity

- Thalidomide is a well-known example
- Prescribed to pregnant women for nausea and insomnia.
- Resulted in over 10,000 births with severe limb malformations.
- Link between exposure and adverse effects was possible because of the potency of the drug and relatively short time period between exposure and manifestation of effects.

Thalidomide-induced birth defects



Reproduction Toxicity Testing

- For small molecules
  - Protocols are standard
  - Covers fertility, embryo-fetal, and pre- and post-natal periods
  - Follow ICH S5R2
- For biotechnology derived pharmaceuticals
  - More case-by-case
  - Study designs evolving based on revisions to ICH S6

In general, animals are good predictors of toxicities in humans

- Thalidomide-like limb abnormalities in monkeys are induced by thalidomide analogs.
- Hormonal agents (e.g. estrogen receptor agonists) and loss of pregnancy

Reproduction Toxicity Testing

- Women of child bearing potential
  - Generally, where appropriate preliminary reproduction toxicity data are available from two species, and where precautions to prevent pregnancy in clinical trials are used, inclusion of WOCBP (up to 150) receiving investigational treatment for a relatively short duration (up to 3 months) can occur before conduct of definitive reproduction toxicity testing.

- Pregnant women
  - Before the inclusion of pregnant women in clinical trials, all female reproduction toxicity studies and the standard battery of genotoxicity tests should be conducted. In addition, safety data from previous human exposure should be evaluated.

Reproduction Toxicity Testing

- Follow ICH M3R2
- Males
  - can be included in Phase I and II trials before the conduct of the male fertility study since an evaluation of the male reproductive organs is performed in the repeated-dose toxicity studies.
  - A male fertility study should be completed before the initiation of large scale or long duration clinical trials (e.g., Phase III trials).
- Women not of childbearing potential
  - Women not of childbearing potential (i.e., permanently sterilised, postmenopausal) can be included in clinical trials without reproduction toxicity studies if the relevant repeated-dose toxicity studies (which include an evaluation of the female reproductive organs) have been conducted.
  - Postmenopausal is defined as 12 months with no menses without an alternative medical cause.

References

ICH Guidances and Guidelines

- fda.gov/cder/guidance or ich.org
  - S1 Carcinogenicity
  - S2 Genetic toxicity
  - S3 Toxicokinetics
  - S4 Duration of Chronic Toxicity Testing
  - S5 Reproductive toxicity
  - S6 Biotechnology
  - S7 Safety Pharmacology
  - S8 Immunotoxicology
  - S9 Nonclinical studies for development anticancer drugs and biologics (under development)
  - M3 Nonclinical Safety Studies for the conduct of Human Clinical Trials
  - Other guidances available from fda.gov

Thank You