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FDA’s Clinical Investigator Course

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U.S. Department of Health and Human Services
Food and Drug Administration
Pharmacology/Toxicology in the Investigator Brochure

Haleh Saber, Ph.D.
Office of New Drugs/CDER/FDA
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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

- Ab-drug conjugate (indication: cancer)
- Cyno monkey was the relevant species
- Findings in monkeys: mainly myelosuppression
- 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
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 eliminates 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 development, i.e. 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
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
Why does FDA not concern itself with potential for drug-induced germ cell mutations?

No agent has been shown to have induced a germ line mutation in a human being.
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

<table>
<thead>
<tr>
<th>Source of carcinogen</th>
<th>Carcinogen</th>
<th>Average daily human exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indoor air</td>
<td>Formaldehyde</td>
<td>598 µg</td>
</tr>
<tr>
<td></td>
<td>Benzene</td>
<td>155 µg</td>
</tr>
<tr>
<td>Tap water</td>
<td>Bromodichloromethane</td>
<td>13 µg</td>
</tr>
<tr>
<td></td>
<td>chloroform</td>
<td>17 µg</td>
</tr>
<tr>
<td>Celery</td>
<td>8-methoxy psoralen</td>
<td>4.9 µg</td>
</tr>
<tr>
<td>Coffee</td>
<td>Catechol</td>
<td>1.3 mg</td>
</tr>
<tr>
<td></td>
<td>Hydroquinone</td>
<td>333 µg</td>
</tr>
<tr>
<td></td>
<td>Caffeic acid</td>
<td>23.9 mg</td>
</tr>
<tr>
<td>Lettuce</td>
<td>Caffeic acid</td>
<td>7.9 mg</td>
</tr>
<tr>
<td>Brown mustard</td>
<td>Allyl isothiocyanate</td>
<td>62.9 µg</td>
</tr>
</tbody>
</table>
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, pre and post natal, and embryo-fetal 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