U.S. FOOD & DRUG ADMINISTRATION

# *Overview of Non-Clinical Safety Assessment in Drug Development*

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# *Drug Review Process*

- **A multidisciplinary, stepwise process involving evaluation of animal and human safety and efficacy data**
- **Evidence of *Safety* and *Efficacy***
- **Pharm/Tox reviewer assesses safety data submitted by sponsor**

# *Definitions*

- **Toxicology: adverse effects of xenobiotics (Casarett and Doull, and Hays).**

- **Pharmacology: the study of drug action. "Embraces the knowledge of the history, source, physical and chemical properties, compounding, physiological actions, absorption, fate and excretion and therapeutic use of drugs" (Goodman and Gilman)**

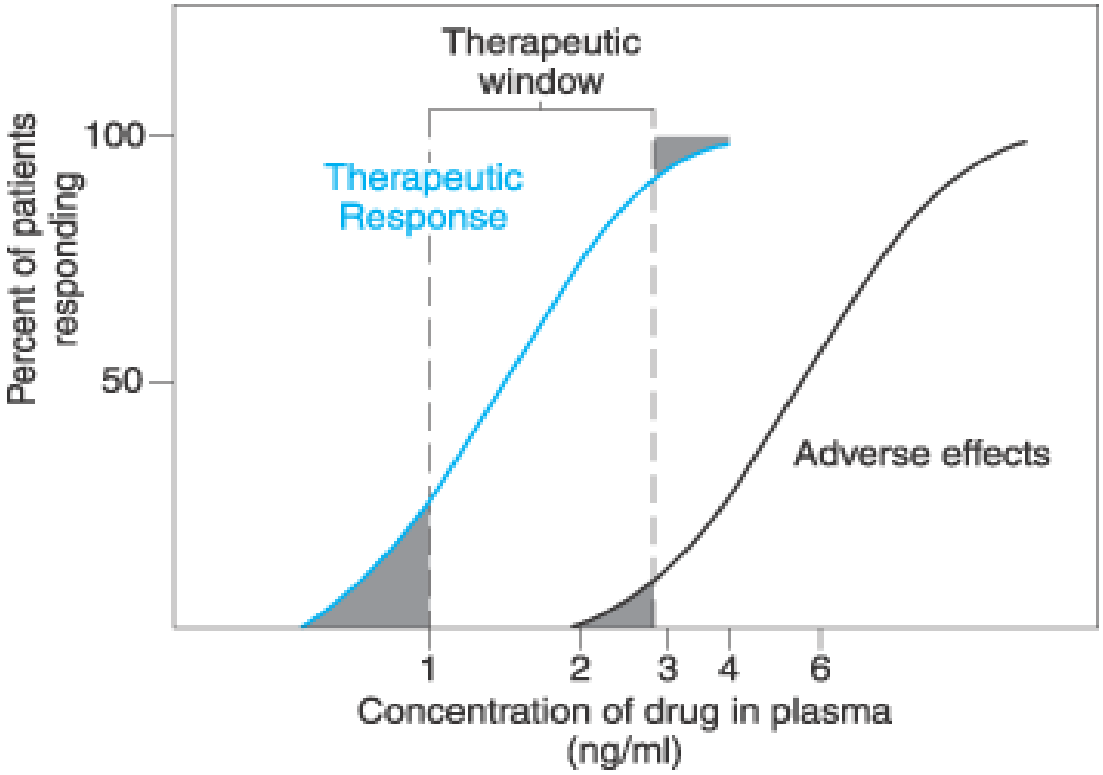
# *Phillipus Aureolus Theophrastus Bombastus von Hohenheim-Paracelsus 1493 – 1541*

**"All substances are poisons; there is none which is not a poison. The right dose differentiates a poison from a remedy."**

**"dosis sola facit venenum"**

**"dosage alone makes the poison"**

# *Therapy versus Toxicity*




***From Goodman and Gilman's The Pharmacological Basis of Therapeutics, 11th edition, 2006.***

# *Pharmacology*

- ***Pharmacokinetics:*** ***what the body does to the drug***
  - **Deals with the absorption, distribution, metabolism, and excretion of drugs.**

- ***Pharmacodynamics:*** ***what the drug does to the body***
  - **The study of the biochemical and physiological *effects* of drugs and their *mechanisms of action*.**

# *What are INDs / NDAs?*

- **Investigational New Drug Applications (INDs)**
  **Request to conduct clinical trials**

  **Are the proposed clinical trials safe? Consider the proposed dose, duration and whether toxicities are monitorable.**

- **New Drug Applications (NDAs)**
  **Request to market a drug**

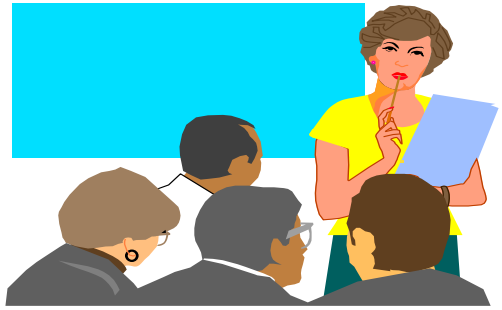
  **Evaluate and convey in the drug label safety data that is only gathered in animals (e.g., reprotoxicity, carcinogenicity)**

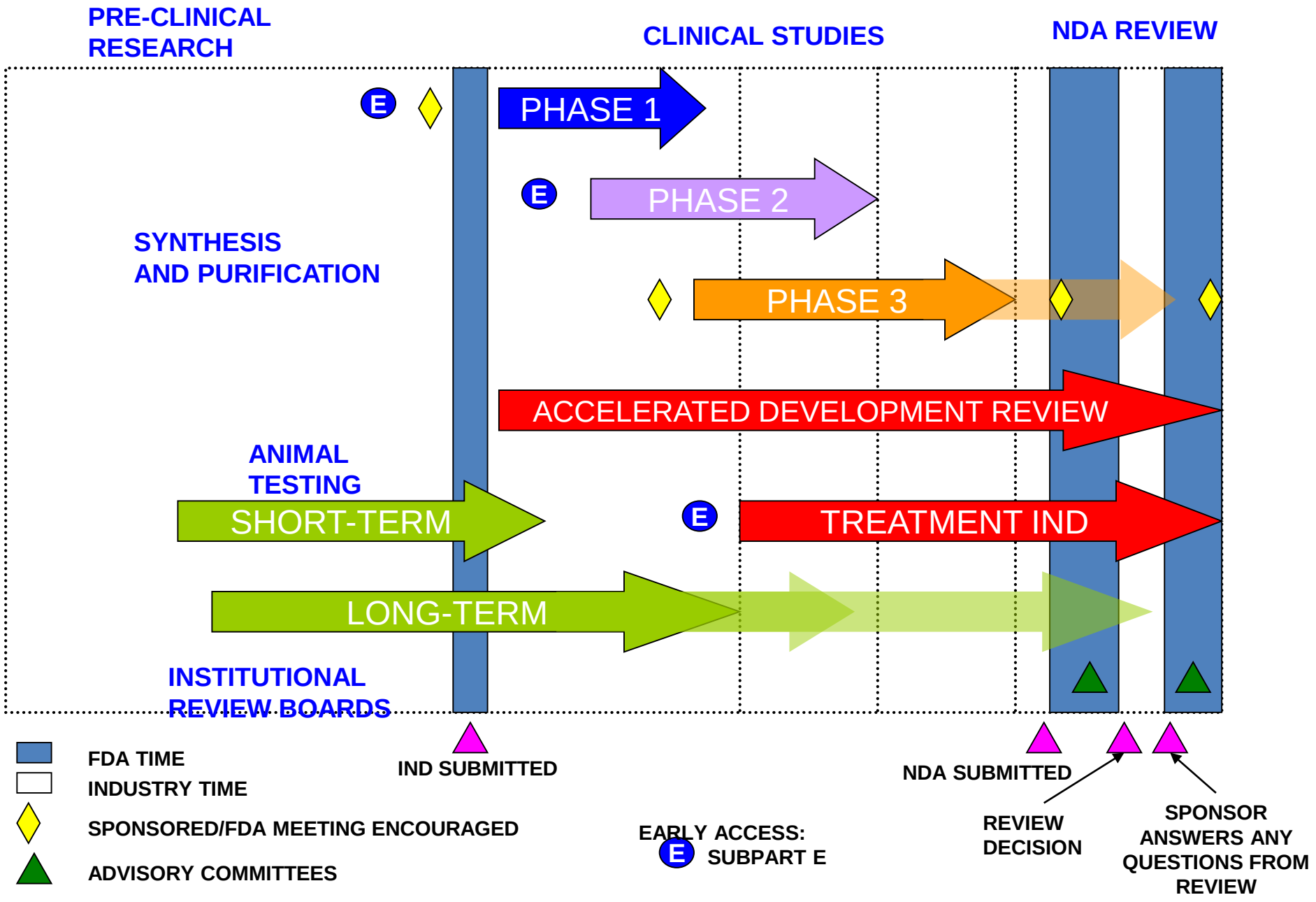
# *What are the Stages of Drug Development?*

- **Pre-IND**
- **IND**
  - ✓**Phase 1 clinical trials**
  - ✓**Phase 2 clinical trials**
  - ✓**Phase 3 clinical trials**
- **NDA**
- **Post-marketing**

# *Pre-IND Meetings*

- **Offer sponsors advice regarding non-clinical development program**
- **Continue dialogue throughout drug development as sponsor gains better understanding of how product will be used clinically (dose, duration, indications for use)**




PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
E
PHASE 1
E
PHASE 2
SYNTHESIS AND PURIFICATION
PHASE 3
ACCELERATED DEVELOPMENT REVIEW
ANIMAL TESTING
SHORT-TERM
E
TREATMENT IND
LONG-TERM
INSTITUTIONAL REVIEW BOARDS
FDA TIME
INDUSTRY TIME
SPONSORED/FDA MEETING ENCOURAGED
ADVISORY COMMITTEES
IND SUBMITTED
EARLY ACCESS: SUBPART E
NDA SUBMITTED
REVIEW DECISION
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW

# *Pharmacology*

- ***In vitro*** **studies to define mechanism of action**
- ***In vivo*** **animal models to demonstrate efficacy**
- **Need not show definitive efficacy to proceed; done more for candidate selection/prioritization**
- **Understanding the pharmacology impacts interpretation of toxicology studies**

# *Types of Non-clinical Studies for Safety Assessment*

GLP

- **Safety pharmacology**
- **Pharmacokinetics**
- **ADME (absorption, distribution, metabolism, elimination)**
- **General toxicology**
- **Local Tolerance**
- **Genotoxicity**
- **Carcinogenicity**
- **Reproductive toxicology**
- **Special studies**

# *The ICH Process*

- **Established in 1990 to improve efficiency of the new drug approval process in Europe, Japan, and the United States**
- **Regulators and industry representatives from all three regions participated**
- **The harmonized topics are safety, quality, and efficacy**

# *Nonclinical Guidances*

**ICH guidance list:**

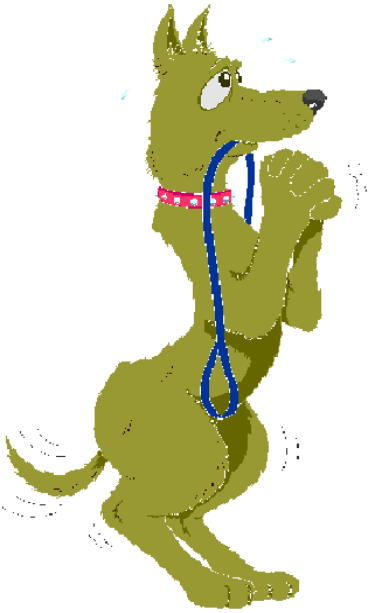
**http://www.ich.org/products/guidelines.html**

**FDA guidance list:**

**http://www.fda.gov/Drugs/GuidanceCompliance**

- **ICH-M3(R2): Nonclinical safety studies for the conduct of human clinical trials for pharmaceuticals**
- **ICH-M7: Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk**
- **ICH-S1B: Testing for carcinogenicity of pharmaceuticals**
- **ICH-S1C: Dose selection for carcinogenicity studies of pharmaceuticals**
- **ICH S2(R1): Genotoxicity testing and data interpretation for pharmaceuticals intended for human use**
- **ICH-S5A: Detection of toxicity to reproduction for medicinal products**
- **ICH-S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals**
- **ICH-S7A: Safety pharmacology studies for human pharmaceuticals**
- **ICH-S7B: Nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals**
- **ICH-S8: Immunotoxicity studies for human pharmaceuticals**
- **FDA Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers**

# *Safety Pharmacology*



- **Investigate potential undesirable pharmacodynamic effects on the physiological function of vital organs**

- **Core Battery**
  - **Cardiovascular system**
  - **Respiratory system**
  - **Central nervous system**

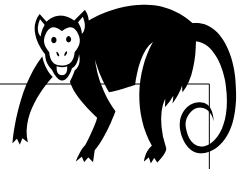
# *Pharmacokinetics / Toxicokinetics*

- **Absorption, Distribution, Metabolism, and Excretion (ADME)**
- **Exposure at different dose levels, including both toxic and non-toxic doses**
- **Metabolites and metabolic pathways**
- **Routes, extent and duration of excretion**
- **Compare with humans**

# *General Toxicity*

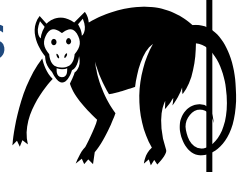
- **Single dose or multiple doses**
- **What are the target organs?**
- **Is there a dose-response for toxic effects?**
- **What is the Maximum Tolerated Dose (MTD)?**
- **What is the No Observed Adverse Effect Level and the No Observed Effect Level Doses (NOAEL and NOEL)?**
- **Is the effect reversible?**

# *Recommended Duration of Repeated Dose Toxicity Studies to Support the Conduct of Clinical Trials*



| Maximum Duration of Clinical Trial | Rodents  | Non-rodents |
|---|---|---|
| Up to 2 weeks | 2 weeks | 2 weeks |
| Between 2 weeks and 6 months | Same as clinical trial | Same as clinical trial |
| > 6 months | 6 months | 9 months |

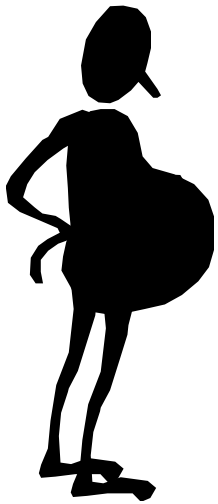
# *Recommended Duration of Repeated Dose Toxicity Studies to Support Marketing*

| Duration of Indicated Treatment | Rodents  | Non-rodents  |
|---|---|---|
| Up to 2 weeks | 1 month | 1 month |
| >2 weeks to 1 month | 3 months | 3 months |
| >1 month to 3 months | 6 months | 6 months |
| > 3 months | 6 months | 9 months |

# *Genetic Toxicity and Carcinogenicity*

- ***Mutagenicity and clastogenicity (short-term in vitro and in vivo tests)***
- ***Carcinogenicity (chronic clinical use of drug, daily or intermittent)***

# *Reproductive Toxicity*



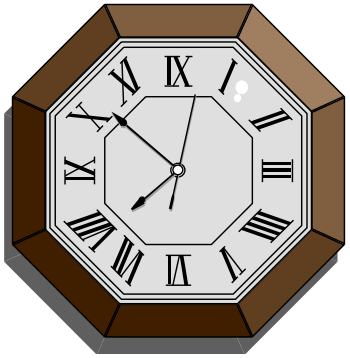
- **Fertility of adult animals**
- **Embryo-fetal development**
- **Postnatal development of offspring, including gross developmental stages and fertility**

# *Special Toxicology*

- **Performed when there is a specific cause for concern based on:**
  - **Mechanism of action**
  - **Drug class**
  - **Signal identified in toxicology studies**

- **Endpoints are limited to those necessary to address the specific concern**

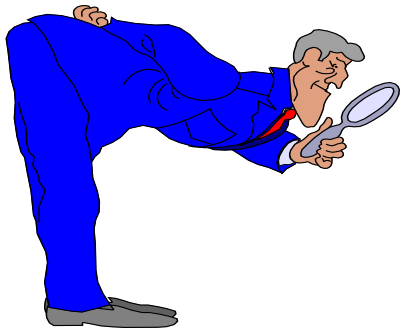
# *Timeline for Pharm/Tox Review*



**Most of the data will be reviewed prior to submission of a New Drug Application (NDA)**

# *Information Needed Before First Human Exposure:*

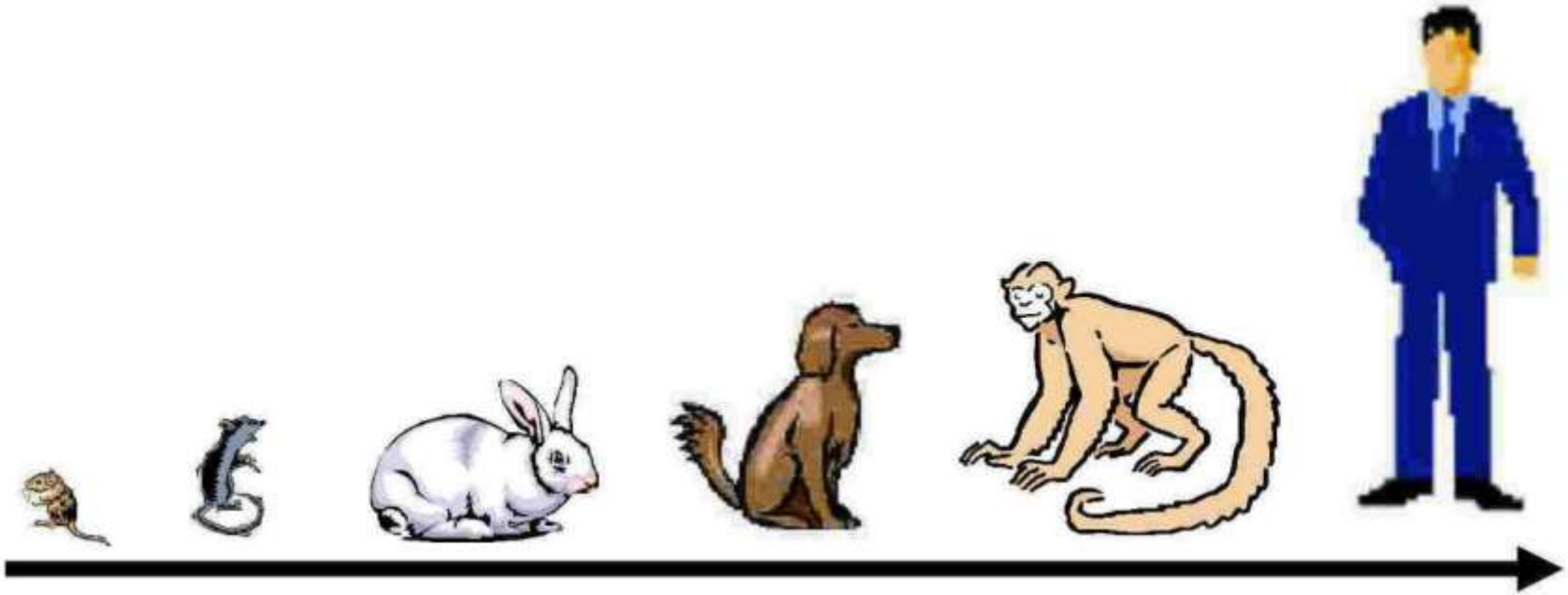
- **Safety pharmacology studies**
- **Acute toxicity (2 mammalian species)**
- **Multiple-dose toxicity (rodent and non-rodent - dose and duration commensurate with proposed clinical trial)**
- **Local tolerance**
- **Genetic toxicity (in vitro studies for mutagenesis and clastogenesis)**



# *Points to Consider*

- **Is an effect observed?**
- **Does it appear to be treatment-related?**
- **Does it appear to be toxicologically significant?**
- **Is it reversible?**
- **Is it likely to be clinically relevant?**
- **Can the effect be monitored?**

# *First In Human Dose*



# *Maximum recommended Starting Dose in humans (MRSD)*

**Major elements needed for maximum recommended starting dose (MRSD) in humans:**

- **Review and evaluate animal data (rodent and non-rodent)**
- **Determine the No Observed Adverse Effect Levels (NOAEL)**
- **Convert NOAEL to human equivalent dose (HED)**
- **Select the most sensitive species or most relevant for assessing human risk**
- **Apply a safety factor (e.g. 10) to increase assurance of safety for the first dose in humans**

# *Determining Safety Factor:*

$$\text{Safety Margin} = \left[ \frac{\text{NOAEL dose in animals, mg/m}^2}{\text{MRHD in Humans, mg/m}^2} \right]$$

MRHD = maximum recommended human dose

# *Calculating HED*

**HED = Animal dose in mg/kg X**

**(animal weight in kg / human weight in kg)$^{0.33}$**

**Table 3: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area**

| Species | Reference Body Weight (kg) | Working Weight Range[a] (kg) | Body Surface Area ($m^2$) | To Convert Dose in mg/kg to Dose in $mg/m^2$ Multiply by $k_m$ | To Convert Animal Dose in mg/kg to HED[b] in mg/kg, Either | |
|---|---|---|---|---|---|---|
| | | | | | Divide Animal Dose By | Multiply Animal Dose By |
| Human | 60 | --- | 1.62 | 37 | --- | --- |
| Child[c] | 20 | --- | 0.80 | 25 | --- | --- |
| Mouse | 0.020 | 0.011-0.034 | 0.007 | 3 | 12.3 | 0.081 |
| Hamster | 0.080 | 0.047-0.157 | 0.016 | 5 | 7.4 | 0.135 |
| Rat | 0.150 | 0.080-0.270 | 0.025 | 6 | 6.2 | 0.162 |
| Ferret | 0.300 | 0.160-0.540 | 0.043 | 7 | 5.3 | 0.189 |
| Guinea pig | 0.400 | 0.208-0.700 | 0.05 | 8 | 4.6 | 0.216 |
| Rabbit | 1.8 | 0.9-3.0 | 0.15 | 12 | 3.1 | 0.324 |
| Dog | 10 | 5-17 | 0.50 | 20 | 1.8 | 0.541 |
| Primates: | | | | | | |
| Monkeys[d] | 3 | 1.4-4.9 | 0.25 | 12 | 3.1 | 0.324 |
| Marmoset | 0.350 | 0.140-0.720 | 0.06 | 6 | 6.2 | 0.162 |
| Squirrel monkey | 0.600 | 0.290-0.970 | 0.09 | 7 | 5.3 | 0.189 |
| Baboon | 12 | 7-23 | 0.60 | 20 | 1.8 | 0.541 |
| Micro-pig | 20 | 10-33 | 0.74 | 27 | 1.4 | 0.730 |
| Mini-pig | 40 | 25-64 | 1.14 | 35 | 1.1 | 0.946 |

[a] For animal weights within the specified ranges, the HED for a 60 kg human calculated using the standard $k_m$ value will not vary more than ±20 percent from the HED calculated using a $k_m$ value based on the exact animal weight.

[b] Assumes 60 kg human. For species not listed or for weights outside the standard ranges, human equivalent dose can be calculated from the formula: HED = animal dose in mg/kg x (animal weight in kg/human weight in kg)$^{0.33}$.

[c] The $k_m$ value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[d] For example, cynomolgus, rhesus, and stumptail.

# *Calculating Safety Factors:*

**Rats**

**NOAEL is 10 mg/kg/day**

**HED = 10 mg/kg x 0.162 = 1.62 mg/kg or (10mg/kg / 6 = 1.6 mg/kg)**

**at mean BW of 60 kg HED = 60 kg x 1.62 mg/kg = 97.2 mg**

**Correct for Safety Factor of 10**

**MRSD in humans = 97.2 mg / 10 = 9.7 or ≈ 10 mg**

**Dogs**

**NOAEL is 5 mg/kg/day**

**HED = 5 mg/kg x 0.541 = 2.7 mg/kg**

**at mean BW of 60 kg HED = 60 kg x 2.7 mg/kg = 162 mg**

**Correct for Safety Factor of 10**

**MRSD in humans = 162 mg / 10 = 16.2 or ≈ 16 mg**

# *Investigational New Drug (IND)*

- **Do dose, duration, route of administration used in non-clinical studies support proposed clinical trial?**
- **Were target organs of toxicity, MTD, and NOAEL identified?**
- **Does product seem "reasonably safe" for proposed trial?**
- **"Hold" may be recommended if data are not adequate or if risk does not appear reasonable for study population**

# *Conclusions - IND*

- **Were the non-clinical studies adequate in terms of dose, duration etc?**
- **Are there sufficient safety margins for identified toxicities to support the proposed clinical trial?**
- **If yes, recommend safe to proceed ☺**
- **If no, recommend clinical hold ☹**

# *As Clinical Trials Proceed...*

- **Longer term toxicity studies may be needed**
- **Genetic toxicity tests should be completed (before phase 2)**
- **As data are collected, animal and human exposure comparisons can be made**
- **Reproductive toxicity tests should be completed (before phase 3)**
- **Carcinogenicity studies may be recommended**
- **Other studies recommended as needed**

# *New Drug Application (NDA)*

- **Review data from outstanding studies or studies not previously submitted**
- **Review label for drug, especially:**
  - **Carcinogenesis, Mutagenesis, Impairment of Fertility**
  - **Pregnancy Category**
  - **Animal Pharmacology and/or Animal Toxicology**

# *Conclusions - NDA*

- **Are the reproductive toxicity and carcinogenicity findings acceptable for drugs to treat this disease?**
- **Have the findings been optimally conveyed in the label?**
- **If yes, recommend approval ☺**
- **If no, recommend non-approval (or label revision) ☹**

# *Post marketing*

- **Usually human data collected after approval of drug**
- **Pharm/tox post marketing requirement (PMR) studies can be included.**

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*Case Study*

# NP-01

# Neuropathic pain

# *IND for Neuropathic Pain*

- **Phase 1 FIH in healthy volunteers to evaluate safety, tolerability and PK in single ascending and multiple doses**
- **50 mg – 200 mg [SAD], MAD TBD x 3 days**
- **Safety pharmacology, genotoxicity, general toxicity studies (7 day oral, 14 day oral in rats and dogs) were submitted**
- **14-day rat (0, 100, 400, 1000 mg/kg/day)**
- **14-day dog (0, 50, 250, 750 mg/kg/day)**
- **FDA had little experience with the CRO which has not been inspected by OSIS**

# *Results*

- **Safety Pharmacology: no drug-related effects.**
- **Genotoxicity: Negative in Ames, Chromosomal aberration and Micronucleus assays.**
- **General Toxicology: Death at the low and mid dose rat study, poor overall condition due to hydration, Vacuolation in nervous system tissues, brain, optic nerve and lesions in lymphoid tissues, liver, kidney lung, and spinal cord**
- **No NOAEL in the rat study.**
- **NOAEL was the low dose in the dog study based on increase CK levels, changes in ECG, decrease in body weight.**
- **The Sponsor suggested that the lesions are associated with dehydration but provided no supporting references.**

# *Safety Factors*

| Species | NOAEL | HED | Proposed Doses | Safety Factors |
|---|---|---|---|---|
| Rat (14-d) | - | - | - | - |
| Dog (14-d) | 50 mg/kg/day | 27.8 mg/kg/day | 50 mg = 0.83 mg/kg<br>100 mg = 1.67 mg/kg<br>200 mg = 3.33 mg/kg | 33x<br>17x<br>8.3x |

# *Hold or No Hold?*

1. **Is the non-clinical safety program sufficient to support the proposed clinical protocol?**

2. **If not (clinical hold), what additional studies are needed?**

# *Reason for Hold*

- **Due to the presence of vacuolation in nervous system tissues, a NOAEL was not established in the 14-day study in rats. Although you attribute the lesions to dehydration, it is not possible to rule out neurotoxicity related to the drug. Therefore, the available non-clinical data is insufficient to support dosing in humans at this time.**

# *What is needed to remove the Hold?*

- **Repeat the 14-day study in rats.**
- **The pathology evaluation should include a peer-review by a board certified pathologist.**
- **A recovery group should be included to demonstrate reversibility of any effects observed.**
- **Explore lower doses to further characterize the exposure-response relationship and attempt to establish an NOAEL.**

# *What is needed to remove the Hold?*

- **Determine whether your drug crosses the blood-brain barrier. This could be accomplished by measuring drug in nervous system tissues from the above mentioned 14-day study in rats or by conducting a radiolabel distribution study.**

- **Provide references or other data to support your conclusion that the vacuolation in nervous system tissues can be attributed to dehydration.**

**The Division Contacted OSIS to inspect the Lab.**

# *Off Hold*

**The Sponsor conducted a follow-up 14-day rat study. In contrast to the potentially adverse effects reported in the initial 14-day rat study at 100 and 400 mg/kg/day (no adverse effects noted at 1000 mg/kg/day; similar clinical exposures across the dose range), there were no adverse effects observed at doses ≤ 100 mg/kg/day.**

**This study was performed in a different CRO.**

# *Safety Factors*

| Species | NOAEL | HED | Proposed Doses | Safety Factors |
|---|---|---|---|---|
| Rat (14-d) | 100 mg/kg/day | 16.1 mg/kg/day | 50 mg = 0.83 mg/kg<br>100 mg = 1.67 mg/kg<br>200 mg = 3.33 mg/kg | 19x<br>9.6x<br>4.8x |
| Dog (14-d) | 50 mg/kg/day | 27.8 mg/kg/day | 50 mg = 0.83 mg/kg<br>100 mg = 1.67 mg/kg<br>200 mg = 3.33 mg/kg | 33x<br>17x<br>8.3x |

# *OSIS Inspection*

- **Most non-clinical studies were performed at XXX CRO. Because there appeared to be little regulatory experience with this laboratory, the review Division requested a GLP inspection by OSIS.**
- **The lab where the second study was conducted, was recently inspected.**
- **Although several concerns were noted and discussed with the laboratory, the OSIS reviewers recommended that the audited study be accepted for Agency review.**

# Questions?

Please complete the session survey:
**surveymonkey.com/r/DRG-D2S03**


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