Overview and Differences in Non-Clinical Safety Assessment for Small Molecule and Biologic Drug Development

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The opinions expressed by Dr. Ghantous in this presentation do not reflect official support or endorsement by the US Food and Drug Administration

Outline

- Stages of Drug Development
- PreIND, IND, NDA/BLA
- Small Molecules vs. Biologics
- Nonclinical studies for safety Assessment
- First in Human Dose
- Case Studies

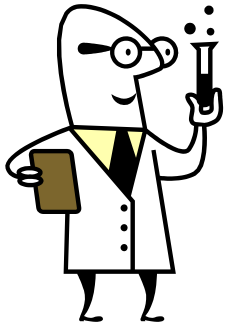
Drug Review Process

- 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

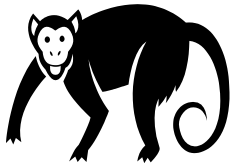
What are the Stages of Drug Development?

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

Pre-IND
Before Submitting an IND, Sponsors…



- Define chemical properties of the drug
- Conduct nonclinical pharmacology/toxicology studies



- Develop clinical protocol(s)

Pre-IND Meetings

- Avoid premature submission of INDs
- Avoid unnecessary nonclinical studies
- Resolve potential safety issues
- Discuss the contents of the IND and overall drug development plan
- Provide regulatory guidance and answer appropriate questions

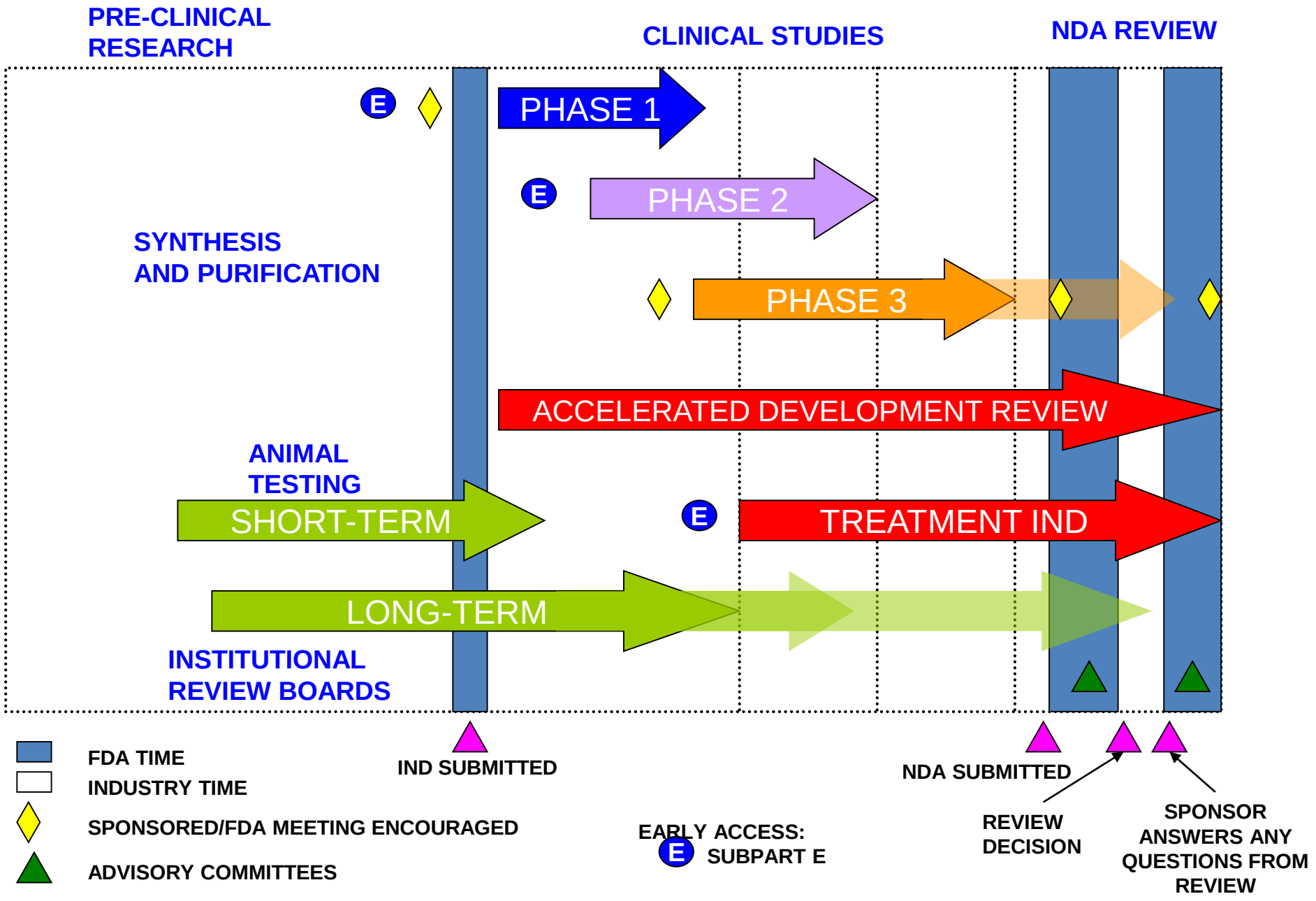
What are INDs / NDAs?

- 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)


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

What are Biologics?

- Biological therapeutics (biologics) can be composed of proteins, sugars, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.
- Biologics are isolated from a variety of natural sources—human, animal or microorganism.
- Unlike chemically synthesized drugs, most biologics are mixtures that tend to be heat sensitive and are susceptible to microbial contamination.

How does FDA regulate biologics?

CBER:

- blood and blood components
- gene and cell therapy products
- human tissue and cellular products used in transplantation
- vaccines

CDER:

- monoclonal antibodies
- cytokines
- growth factors
- enzymes
- immunomodulators

Biologics vs. Small Molecules

Biologics	Small Molecules
Large and Complex	Small and uniform
High immunogenicity potential	Low immunogenicity potential
Highly targeted	Less targeted
Species specific	Species independent
Catabolized/degraded	Metabolized
Small volume of distribution	Large volume of distribution
Parenteral routes	Oral and parenteral routes

Biologics are large Molecules

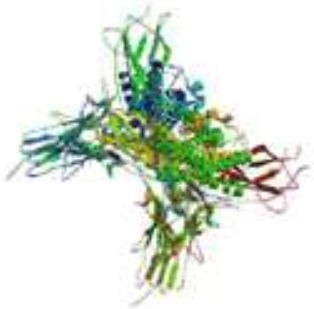
Figure 1
Chemical Structure Comparisons of Select Medications

Acetaminophen

151 daltons

Atorvastatin

558 daltons



Filgrastim

18,880 daltons

Epoetin alfa

30,400 daltons

Rituximab

145,000 daltons

Coagulation Factor VIII

264,400 daltons

3dchem. Available at: http://www.3dchem.com/molecules.asp?ID=19

The European bioinformatics institute. Available at: http://www.ebi.ac.uk/

The Drugbank. Available at: http://www.drugbank.ca/druos/DB00073

Expression therapeutics. Available at: http://www.expressiontherapeutics.com/hemophilia

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*.

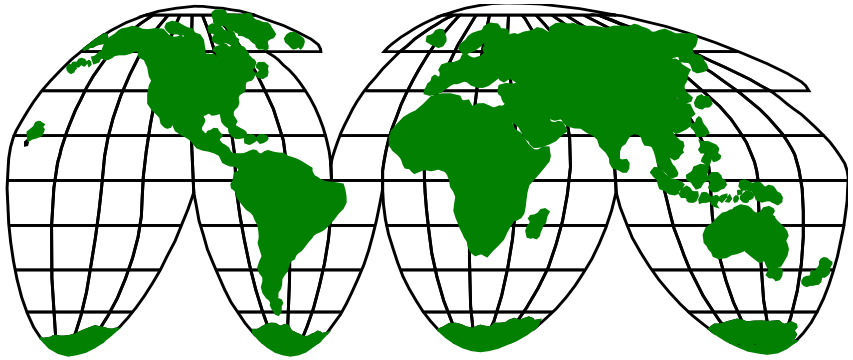
Types of Non-clinical Studies for Safety Assessment

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:

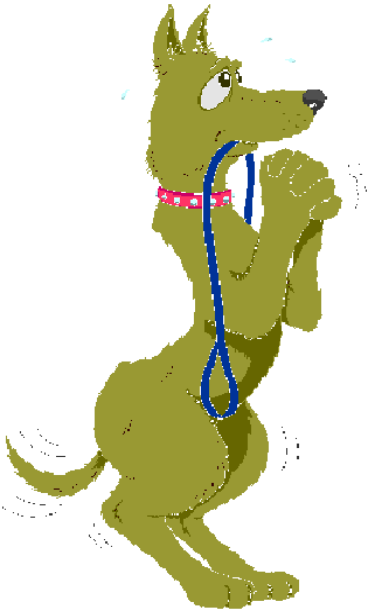
http://www.ich.org/products/guidelines.html

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

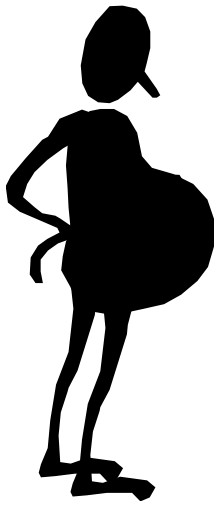
Recommended Duration of Repeated Dose Toxicity Studies to Support Marketing

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

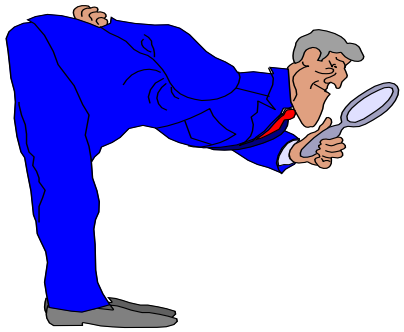


- Fertility of adult animals
- Embryo-fetal development
- Postnatal development of offspring, including gross developmental stages and fertility

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



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?

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)

Types and Timing of Nonclinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Pharmacodynamics	Prior to Phase 1	Yes	Yes
In vitro metabolic profile and plasma protein binding	Prior to Phase 1	Yes	No
Systemic exposure	Prior to Phase 1	Yes	Yes
Comparative *in vivo* animal and human metabolism data	Generally prior to Phase 3	Yes	No

*Reflects ICH M3(R2), 2009

Types and Timing of Nonclinical Studies

Study Type	(Relative to Clinical Trials)	Small Molecule	Biologic
Safety pharmacology • Cardiovascular • Respiratory • CNS	Prior to Phase 1	Yes	Product specific
General toxicology	Prior to Phase 1, 2, and 3	Yes (two species)	Yes (one species acceptable)

Types and Timing of Nonclinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Genotoxicity • Bacterial mutation • *In vitro* chromosomal aberrations • *In vivo* chromosomal aberrations • *In vivo* micro nucleus	• Prior to Phase 1 • Prior to Phase 1 • Prior to Phase 2	Yes	Generally no

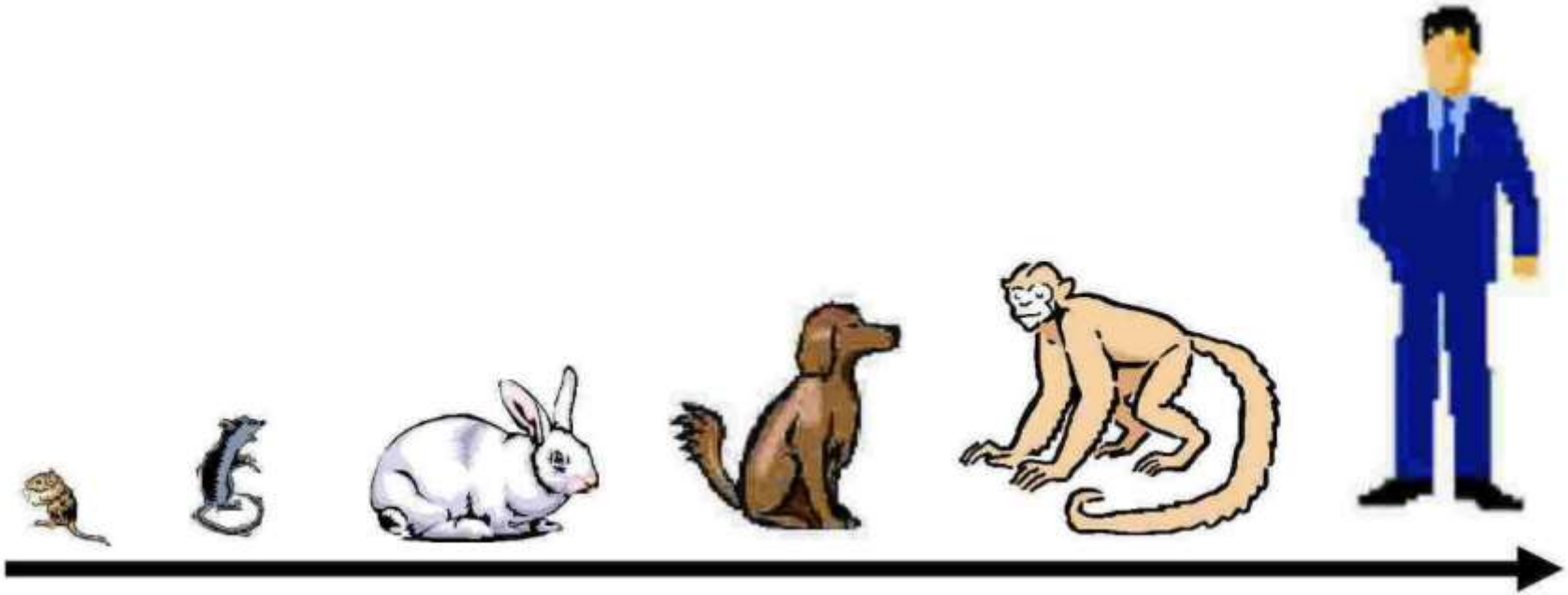
Types and Timing of Nonclinical Studies

Study Type	Timing (Relative to Clinical Trials)	Small Molecule	Biologic
Reproductive Toxicology • Embryo-fetal development • Male fertility • Female fertility • Pre-/postnatal development	• Prior to Phase 3 • Prior to Phase 3 • Prior to Phase 3 • Marketing approval	Generally Yes	Product specific
Carcinogenicity	Marketing approval	Yes (chronic drugs)	Product specific

Nonclinical Programs for Small Molecules

Study Type	Oral	Dermal	Ocular
General toxicology	Rat and dog	Mini-pig (dermal) Rat (systemic)	Rabbit, pig, dog, monkey (ocular) Rat/nonrodent (systemic)
Genotoxicity	Yes	Yes	Yes
Safety Pharmacology	Yes	Generally yes, but consider systemic exposure and body surface area	Not routinely expected
Melanin Binding	Not routinely	Not routinely	Generally yes
Photosafety	As needed	As needed	As needed
Hypersensitivity	Not routinely	Yes	Not routinely
Reproductive toxicology	Yes	Yes	Might be able to waive some studies
Carcinogenicity	Yes	Yes	Might be able to waive

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:

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

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

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 (no more)
  - 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 were submitted
- 14-day rat (0, 100, 400, 1000 mg/kg/day)
- 14-day dog (0, 50, 250, 750 mg/kg/day)
- CRO which has not been inspected by OSIS

Results

- 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.

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

- Vacuolation in nervous system tissues.
- 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.

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, 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 100 mg = 1.67 mg/kg 200 mg = 3.33 mg/kg	19x 9.6x 4.8x
Dog (14-d)	50 mg/kg/day	27.8 mg/kg/day	50 mg = 0.83 mg/kg 100 mg = 1.67 mg/kg 200 mg = 3.33 mg/kg	33x 17x 8.3x

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Case Study

FLU

Treatment of severe complicated influenza A disease

- MOA: monoclonal antibody against influenza A hemagglutinin.
- Open-Label, Dose-Escalation Phase 1 Study in Healthy Volunteers to Evaluate the Safety and Pharmacokinetics.
- 2 mg/kg, 5 mg/kg, 15 mg/kg, 30 mg/kg, and 50 mg/kg
- IV infusion, single-dose

Results

- Main Study (mice) – 4 total IV doses on Days 1, 2, 7, 14
- Dose Levels – 5, 50 and 250 mg/kg
- Recovery – 4 weeks
- Mortality – 14 early deaths at 5 mg/kg (5/102; 1 male, 4 females) and 50 mg/kg (9/102; 3 males, 6 females).
- No early deaths at 250 mg/kg
- Deaths occurred after 4th dose on Day 14 within 1-2 hours of dosing.
- Cause of death was not determined but likely anaphylaxis.

Concerns

- Adverse immune response or anaphylaxis based on the dose response.
- No follow up work to confirm or demonstrate the deaths were in fact related to an adverse immune response.
- The tissue cross reactivity studies showed membrane binding to the colon, small intestine, and fallopian tubes.
- The sponsor argues that because the human and mouse showed similar tissue binding and no toxicity was seen in the mouse at the high dose of 250 mg/kg (5X higher than the proposed high dose of 50 mg/kg in the Phase 1 clinical trial), that the off-target binding is not relevant in vivo.

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

- Death at the low and mid dose but not the high dose
- Anaphylaxis effect?
- Off target binding, GI, Follopian tubes, adrenals, bladder, kidney

What is needed to remove the Hold?

- Conduct an additional toxicology study in another species (e.g., rat) with similar tissue binding as human.
- If anaphylaxis is observed, endpoints could include the measurement of immune complexes, immunoglobulins, markers of anaphylaxis (e.g., platelet activating factor, serum tryptase, histamine), complement activation markers, and cytokine release.
- The duration of such a study should be longer than the 14-day toxicity study to ensure coverage for the anticipated longer half-life in humans.

Questions?

Please evaluate this session:

surveymonkey.com/r/DRG-D1S04


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