Limit the Use of the Non-Rodent in Toxicity Testing: Scientific Considerations

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Toxicity Testing Paradigm*: Science-Based or Based on Tradition?

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J Trevan the ‘inventor’ of LD50 in mice-
Pharmacologists branching into
toxicology: acute testing should be done
in several species

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H Schlossmann: acute toxicity in
mice/rats followed by a few guinea
pigs, rabbits, cats, dogs, etc.

1944
FDA/AMA (JAMA):
Subacute: 1 or more species
Chronic: 3 or more species
(toxicologists choice of species)

1965
AJ Lehman of FDA presents guidelines
in a lecture that more or less became
official: 2 species- one a non-rodent

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PMA Drug Safety Section
(unofficial):
2 or more species: usually
rat and beagle dog

The necessity to use a rodent and a non-rodent
in all toxicological experiments was now clearly
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European Society for the Study of Drug Toxicity concurs and selects species: rat and dog

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Guidance for Industry
M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals

2 mammals: 1 a non-rodent

*Zbinden G., Reg Tox and Pharmcol 17:85, 1993
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals*

71% Overall Concordance [true positive]

63% Non-Rodent

43% Rodent

Multinational Pharmaceutical Company Survey/ILSI Workshop - better understand concordance of toxicity observed in humans with that observed in experimental animals

*Olson H, et al, Reg Tox Pharm 32:56, 2000
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

Safety Pharm Concordance (Dog telemetry, n= 14 studies*)

Concordance Excluding Single Dose Safety Pharm Non-Rodent studies:

General Toxicity

*Olson H, et al, Reg Tox Pharm 32:56, 2000
Non-Rodent Safety Pharmacology Studies

- Telemetered non-rodents (usually the dog) for detailed ECG, Blood Pressure and Respiratory Parameters
- Endpoints have good predictivity
- Minimal animal usage (n=4/study)
- Animals re-used for many compounds
- Safety pharmacology concordance enhances overall non-rodent numbers
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

Safety Pharm Concordance (Dog telemetry, n= 14 studies*)

GI Tox Prediction by non-rodent
- high correlation
- expected pharmacology
- ‘nuisance’ effects in the clinic

*Olson H, et al, Reg Tox Pharm 32:56, 2000
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals
Better understanding of non-rodent data…

Even Playing Field
Moving Forward: Prospects for Reducing and Refining the Use of Non-rodents in Regulatory Toxicity Testing of Pharmaceuticals

- Expand utilization of the Exploratory IND
- Re-examine the value of including *routine* reversibility
- Proactively incorporate newer technologies and tissue injury biomarkers
- Reduce the number of non-rodent studies conducted
- Embrace the 3 R’s
Expand Utilization of the Exploratory IND (Exp-IND)

• Part of FDA’s Critical Path Initiative
• FDA stated goal: allow for reduction of time and resources expended on candidates *unlikely to succeed* (8% chance to reach market)

• A clinical trial that:
  – is conducted early in Phase I (prior to traditional dose escalation)
  – involves very limited human exposure
  – involves limited duration of dosing
  – is not intended to establish MTD

http://www.fda.gov/cder/guidance/index.htm
Exp-IND Studies: **Advantages**

- Significant potential for conserving resources
- Evaluate PK and/or PD properties
- Test for Drug-Drug interactions
- Test for Proof of Concept
- Validate preclinical animal efficacy model
- Determine bio-distribution characteristics using imaging technologies

**Types of Studies**

- Single or multiple-dose
- Sub-pharmacologic or pharmacologic dose
- Designed for pharmacologic or PD endpoints

*Exp-INDs represent efficient way to drive early candidate selection (internal decision making)*
Exp-IND

Preclinical Toxicity Testing

Two-week toxicity study in sensitive species (rodents)
  • Should allow determination of NOAEL

Study in non-rodent
  • to confirm that rodent is most sensitive species
  • reduced number of animals (e.g. n=2/gender, one dose group, no controls)
  • may allow single non-rodent gender if no gender difference observed in rodent study, or if only single gender is to be evaluated in the clinical trial

Exp-IND

One approach to reduce non-rodent use
Re-Examine the Value of Including *Routine* Reversibility

For example: anti-cancer compounds with mode of action being cell cycle disruption, induce bone marrow (BM) suppression, GI villous atrophy, and/or individual cell necrosis of various organs.

- These findings have been demonstrated many times over to be reversible (and are expected based on pathology fundamentals).
- Evaluation of reversibility should be addressed only when it cannot be deduced following histopathology evaluation.
Proactively Incorporate Newer Technologies and Tissue Injury Biomarkers: Magnetic Resonance Imaging (MRI) with Biomarkers to Monitor Non-rodent Target Organ Toxicity

MRI Non-Invasive Biomarker of Organ Injury + Traditional and *Novel* Biomarkers = ‘Real-Time’ Longitudinal Toxicity Assessment

- Reduced ‘read out’ time (vs histopath)
- Assess reversibility (w/o increased N)
- Defer chronic study; optimize use of non-rodent

Translation Bridging Biomarkers [Support Clinical]

Knowledge Information
- Systems Toxicology
- Traditional Endpoints
- ‘Omics’ initiatives
- In Vitro
Consider Reducing the Number of Studies Conducted

- Use only the rodent for longer term studies (sensitive species)
  - Vast majority of animal/human toxicity concordance observed in studies of $\leq 1$ mo
- Conduct only 1 short term and 1 long term non-rodent study for a NCE; use in-life data and biomarkers to extend dosing in the clinic
Consider Reducing the Number of Studies Conducted

• Re-visit Regulatory Guidance’s
  e.g. FDA Excipient Regulatory Guidance
  – *Stand alone* studies for novel excipient?
  – Both Rodent *and* Non-rodent Studies?
  – Need to achieve *MTD*?
  – Need to conduct subchronic *and* chronic studies?
The 3 R’s: Replacement, Reduction, and Refinement

Important step taken to reduce animals used in specific safety test for new medicines

EU urged to review animal testing
The EU Commission has released a draft protocol on Animal Welfare..

Plan Expedites Alternatives to Animal Testing

NIH Collaborates with EPA to Improve the Safety Testing of Chemicals
New Strategy Aims to Reduce Reliance on Animal Testing
Summary: Limit the Use of the Non-Rodent in Toxicity Testing

• 1st must ensure subjects do not face undue risk of harm

• Non-rodent safety pharm endpoints provide important human risk information with minimal animal use

• Rodents have similar concordance for general toxicity endpoints as do non-rodents

• Must utilize new approaches [exp-IND, biomarkers] to help proactively address the 3 R’s

• Need to use more science-based study designs rather than continue with ‘tradition’