SOT 48th Annual Meeting
& ToxExpo™

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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?

1927 1937 1944 1965 1977

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

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

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

joint governmental and private effort to provide guidelines for testing was abandoned

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

European Society for the Study of Drug Toxicity concurs and selects species: rat and dog

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 established !*

*Zbinden G., Reg Tox and Pharmcol 17:85, 1993

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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

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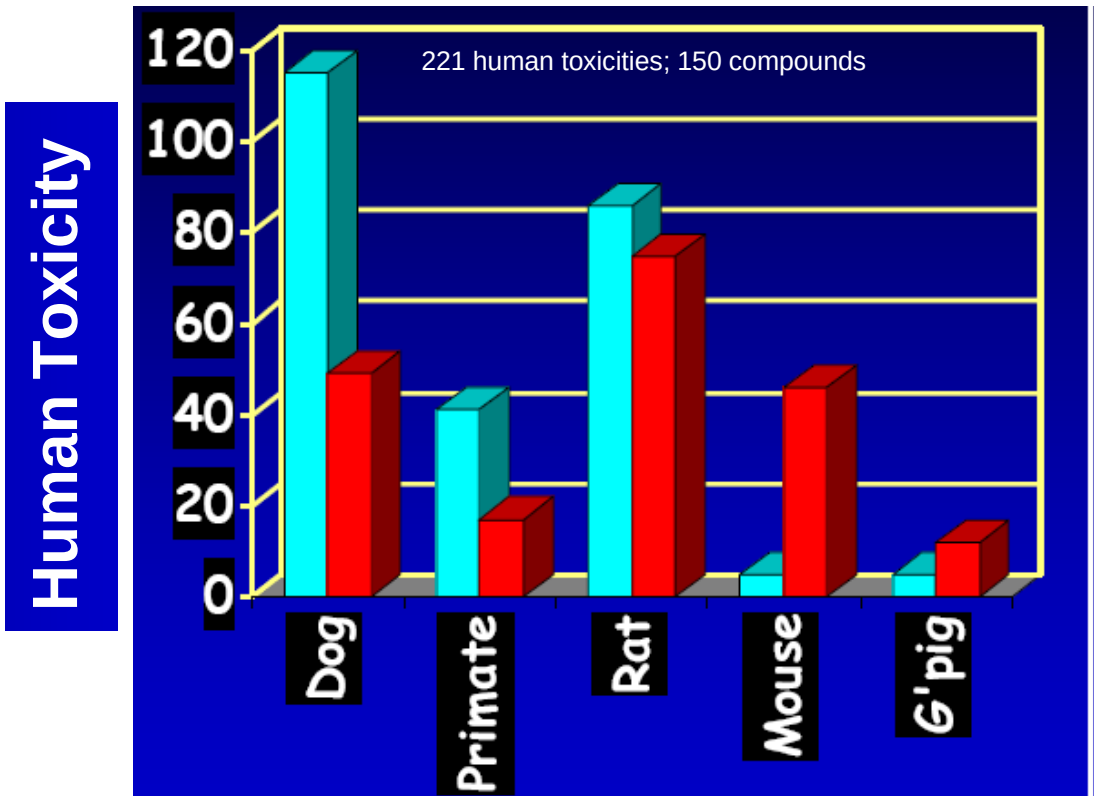
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals*



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

71% Overall Concordance
[true positive]

63% Non-Rodent

43% Rodent

*Olson H, et al, Reg Tox Pharm 32:56, 2000

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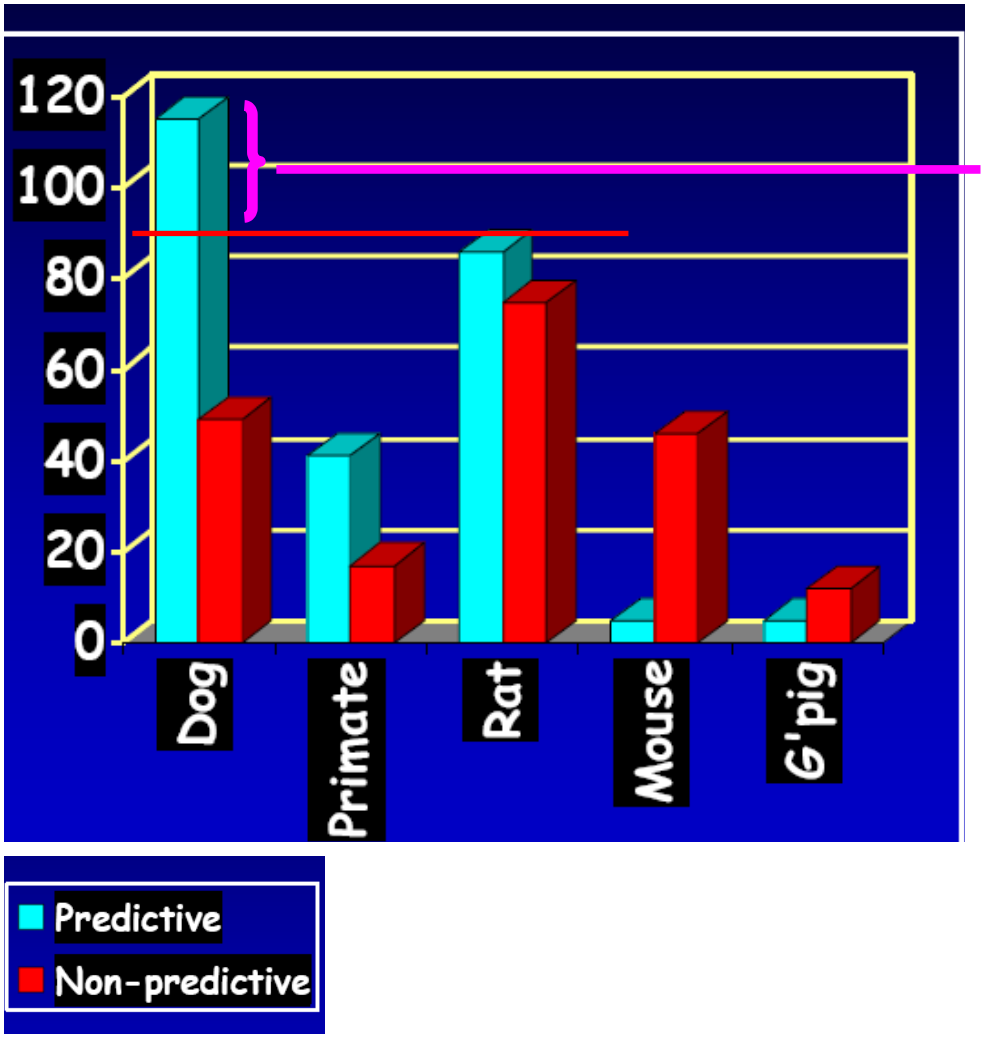
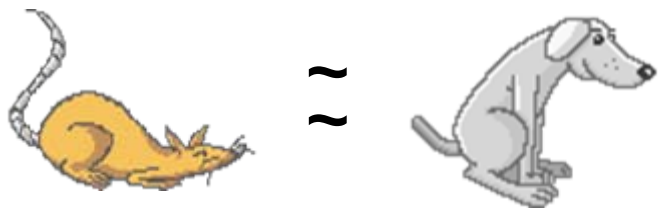


Safety Pharm Concordance (Dog telemetry, n= 14 studies*)

Concordance Excluding Single Dose Safety Pharm Non-Rodent studies:



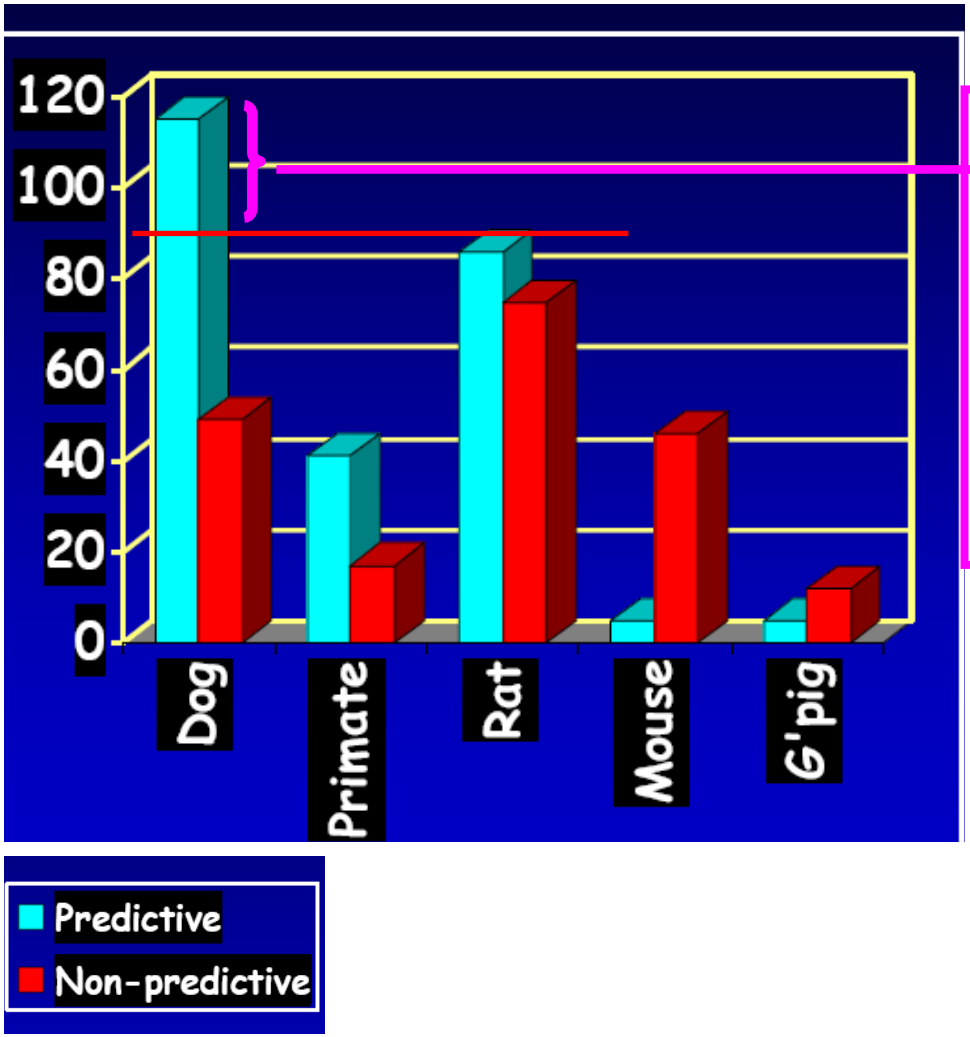
General Toxicity

*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…

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

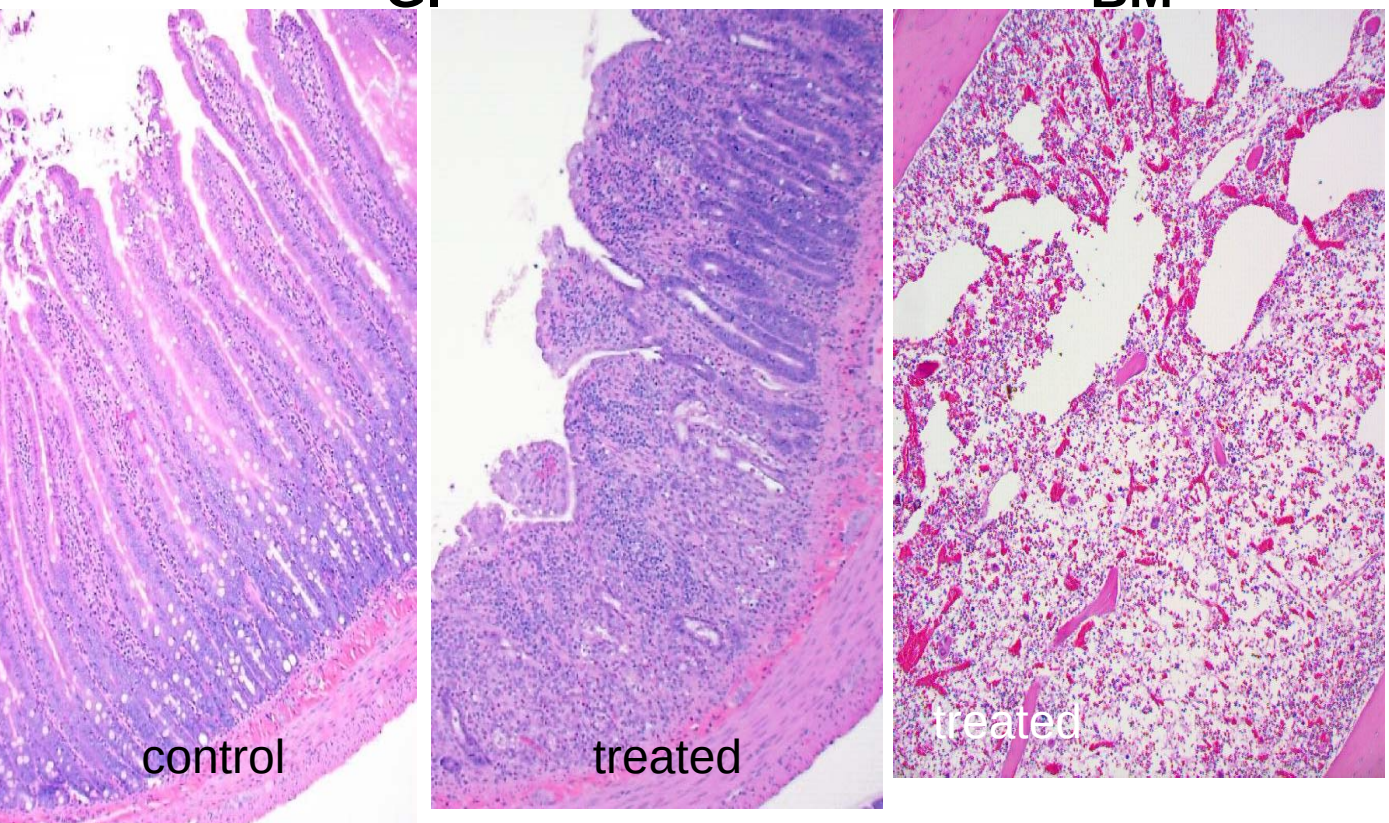
- to confirm that rodent is most sensitive species
- reduced number of animals (e.g. n=2/gender, one dose group, no controls)
- may allow single non-rodent gender if no gender difference observed in rodent study, or if only single gender is to be evaluated in the clinical trial

Exp-IND
One approach to reduce non-rodent use

Re-Examine the Value of Including *Routine* Reversibility

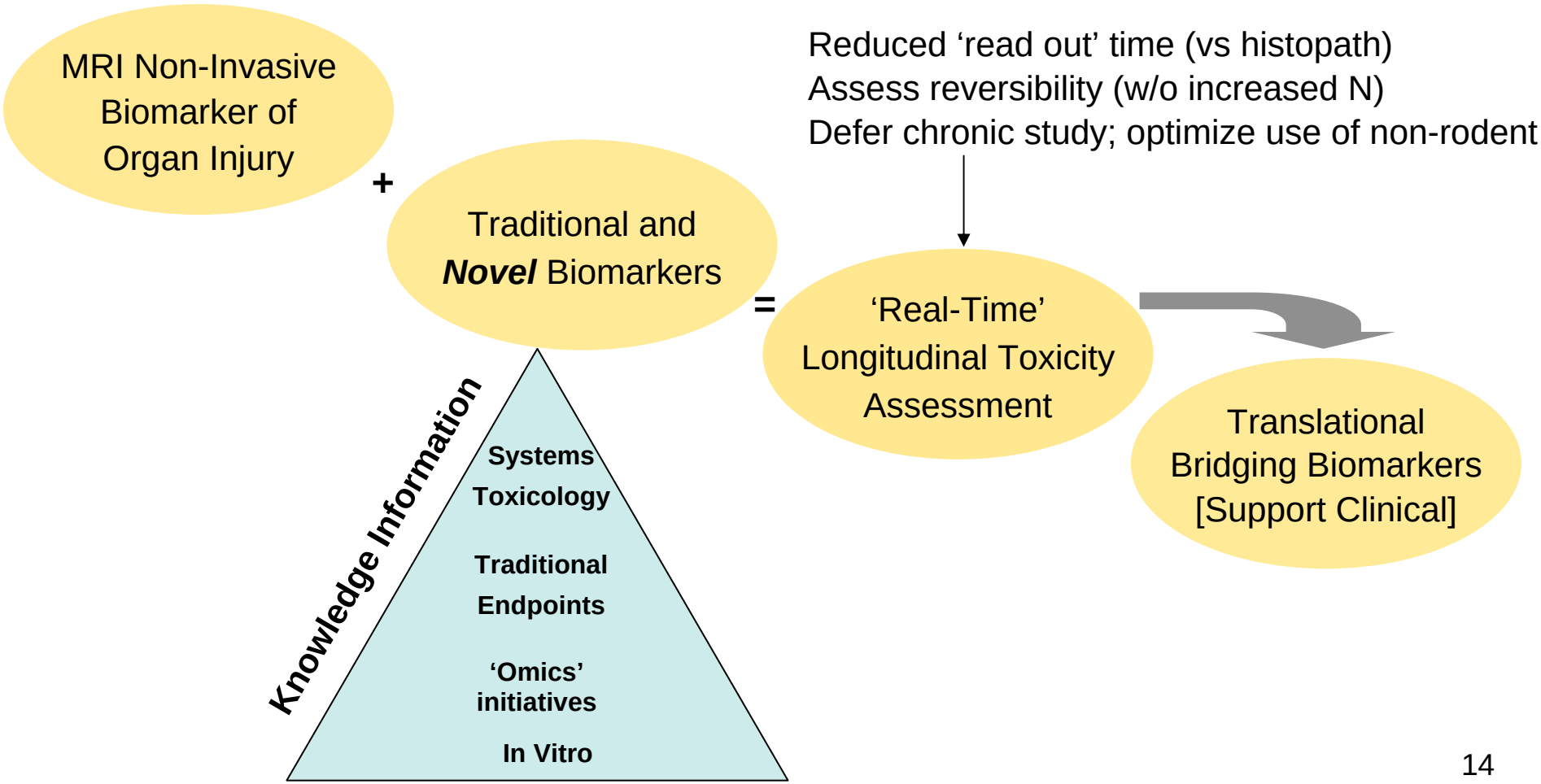
For example: anti-cancer compounds with mode of action being cell cycle disruption, induce bone marrow (BM) suppression, GI villous atrophy, and/or individual cell necrosis of various organs

GI **BM**



- 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



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 ≤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

American College of Laboratory Animal Medicine

NC3Rs

National Centre for the Replacement, Refinement and Reduction of Animals in Research

efpia

European Federation of Pharmaceutical Industries and Associations

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..

National Institutes of Health

The Nation's Medical Research Agency

Plan Expedites Alternatives to Animal Testing

EPA

www.epa.gov

science in ACTION

BUILDING A SCIENTIFIC FOUNDATION FOR SOUND ENVIRONMENTAL DECISIONS

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'