Eminent Toxicologist Lecture Series
Regulatory Toxicology

Society of Toxicology
Eminent Toxicologist Lecture Series

Regulatory (Pharmaceutical) Toxicology

Ruth Roberts
Director, ApconiX Ltd
Chair of Drug Discovery, University of Birmingham, UK
Ruth Roberts is co-founder and co-director of Apconix, an integrated toxicology and ion channel research company that provides expert advice on nonclinical aspects of drug discovery and drug development to academia, industry, government and not-for-profit organisations.
Overview/Objectives

- Outline and purpose of regulatory toxicology testing for pharmaceuticals
  - Overall design of the package from first time in humans (FTIH) through to marketing authorisation
  - Purpose: ensuring volunteer and patient safety in clinical trials
  - Decision making

- General Toxicology
  - Maximum tolerated dose (MTD)/Dose Range Finding (DRFs), “pivotal” and chronic toxicology studies
  - Design (doses, species, duration) and outcome
  - Regulatory documentation

- Outline of general toxicology testing for agrochemicals and general chemicals

- Challenges and opportunities
  - Translation
  - Attrition
  - Assumptions to challenge
  - In vitro replacements

- Future Perspectives
Understand the purpose of pharmaceutical toxicology
Understand the pivotal role played by general toxicology studies in protecting volunteer and patient safety
Understand common principles with other sectors (agrochemicals, general chemicals)
Understand outcome of general toxicology studies and the principles and caveats of their designs
Understand the global framework provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
Understand the scope for scientific interpretation (guideline versus “rules”)
Have a perspective on challenges to the current paradigm of toxicology testing in support of regulatory submissions
Orientation: Clinical Development of a New Drug

**Discovery**
- Target selection (TS)
- Lead generation (LG) and optimisation (LO)
- Candidate drug (CD) prenomination

**Development**
- Good Laboratory Practice (GLP) Toxicology Phase
- Phase I
- Phase II
- Phase III
- Phase IV

**Phase I:** Healthy volunteers usually male, tolerance, kinetics, pharmacology (proof of mechanism)

**Phase II:** Early patient studies, tolerance, kinetics, pharmacology, efficacy (proof of concept), dose range, drug interactions, special patient populations

**Phase III:** Data for registration via double-blind trials against competitors on efficacy and safety

**Phase IV:** Post marketing surveillance and market positioning

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Aim of Preclinical Testing is to Determine Safety Margins

Safety margin (SM) calculation:

Exposure at the NOAEL = SM

Predicted exposure required for clinical efficacy

For benign indications, 100-fold margin may be appropriate
For terminal conditions, much lower margin may be acceptable
• Preclinical data are critical for the FTIH decision

• Clinical safety data become increasingly important as clinical trials progress

• Human data outrank nonhuman data in assessing human safety!
Discovery and Development Toxicology

Regulatory requirement

- Traditionally the ‘home’ of pharmaceutical toxicology
- Provide safety information on one compound to allow entry into clinical trials and its registration and prescription
- Establish whether inherent toxicity is acceptable for the patient population
- Problem solve any findings: MOA and relevance to humans?

Project-specific requirements

- May have multiple lead series and test molecules for each
- Identify early the safety risks associated with target and chemistry in patient setting
- Influence chemical design and selection to avoid issues where possible
- Design unique experimental plan to assess and mitigate target or chemistry risks

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ICH: International Council for Harmonisation
‘…..Interpretation and application of technical guidelines for drug registration……. A unique undertaking that brings together the drug regulatory authorities and pharmaceutical industry of Europe, Japan and the US’.
Regulatory Toxicology Testing of a Small Molecule Drug

Abbs: CD: candidate drug; CNS: Central Nervous System; DRF: dose range finding; EFD: Embryo Fetal Development; FTIH: first time in human; GLP: good laboratory practice; LG/LO: lead generation/lead optimisation; ICH: International Council for Harmonisation; MOLY: Mouse Lymphoma; MTD: maximum tolerated dose; P&P: peri and post natal; SAR: Structure Activity Relationship; TS: target selection
Support of Clinical Trials: Regulatory and Scientific Considerations

- Disease specific considerations: life threatening?
- Duration of clinical use: daily versus single dosing
- Target populations: post-menopausal, children, males/females?
- Specific studies triggered by special uses: antigenicity, local tolerance, dependency?
Translating Regulatory Guidance into Preclinical Studies: Safety Evaluation of a New Small Molecule

- **Formulation**
  - stability/homogeneity, etc.

- **General Toxicology**
  - Acute studies (some countries)
  - Dose Range Finding (DRF) studies in rats & dogs
  - 1-month studies in rats & dogs
  - 6-month studies in rats and dogs
  - 9-month/1-year study in dogs

- **Oncogenicity**
  - sighting study and transgenic study in the mouse
  - 2-year studies in the rat

- **Genetic toxicology**
  - Ames test
  - Micronucleus test
  - mouse lymphoma assay

- **Reproductive toxicology**
  - Preliminary teratology studies in rabbits
  - Teratology studies in rats and rabbits
  - Fertility study in the rat
  - Peri- and postnatal study in the rat

- **Safety/General Pharmacology**

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Focus on the General Toxicology

General toxicology
As specified in ICH M3 (R2), S9, S4

MTD/DRF: Maximum tolerated dose/dose range finding
Considerations:

1. There could be limited amount of compound
2. It’s usually key to demonstrate MTD for the regulatory package
3. Skilled observation of early days of a study are crucial
4. Generally start rodent before nonrodent in case of unexpected issues
5. An “intended therapeutic dose” is likely to “evolve” with clinical experience
6. A well-designed nonclinical package informs and gives maximum flexibility to an evolving clinical plan
Clinical Development of a New Oncology Drug: Options

Discovery

- TS
- LG/LO
- CD prenomination

GLP Toxicology Phase

Development

- Phase I: patients, scheduling with current Standard of Care

20+ cohorts

Bespoke nonclinical studies on combinations, schedules, intervals

Each cohort is on average 3 patients; $80 000/patient

Obligation to gain maximum knowledge from each patient
Species Selection

• Two species=regulatory requirement (historically, mainly rat and dog)
• Other species may be used if data suggest they are more appropriate
  – Biological relevance
  – Bioavailability
• Non-human primates or minipigs recognised alternative non-rodent species
• Increasing use of minipigs over dog
• Biotechnology compounds tend to use primates
• Use young, healthy animals
**Typical First Time in Humans (FTIH) Study Design**

**Rodent (n supports statistics)**
- Control: 10Males + 10Females
- Low dose: 10M + 10F
- Medium dose: 10M + 10F
- High dose: 10M + 10F

28 days

**Non-rodent (no stats)**
- Control: 3Males + 3Females
- Low dose: 3M + 3F
- Medium dose: 3M + 3F
- High dose: 3M + 3F

28 days

**In-life observations**
- Macroscopic observations
- Pathology
- Clinical chemistry

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A Typical FTIH Package also Includes Recovery

Rodent
- Control: 10M + 10F
- Low dose: 10M + 10F
- Medium dose: 10M + 10F
- High dose: 10M + 10F

Non rodent
- Control: 3M + 3F
- Low dose: 3M + 3F
- Medium dose: 3M + 3F
- High dose: 3M + 3F

28 days

In-life observations
Macroscopic observations
Pathology
Clinical chemistry

28 days
General Toxicology under ICH M3/ICH S9

- Outcome: target organ toxicities in first time in man (FTIM) studies and chronic studies
  - What are the most common target organs in FTIM general toxicology studies?
  - Does this differ by species?
  - An analysis of 77 AstraZeneca drugs
FTIM Target Organ Profiles – Rodent (78 studies)

Horner et al (2013)
*Regulatory Toxicology and Pharmacology*, 65, 334-343.
FTIM Target Organ Profiles — Non-Rodent (77 studies)

Horner et al (2013)
Regulatory Toxicology and Pharmacology, 65, 334-343.
# Liver Is the Most Frequent Target Organ in Rodent and Non-Rodent FTIH Studies

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Non-rodent</th>
<th>Rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Liver</td>
<td>Liver</td>
</tr>
<tr>
<td>2</td>
<td>Thymus</td>
<td>Adrenal</td>
</tr>
<tr>
<td>3</td>
<td>GI</td>
<td>Spleen</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidneys, Kidneys</td>
</tr>
<tr>
<td>4</td>
<td>Testes</td>
<td>Bone Marrow</td>
</tr>
<tr>
<td>5</td>
<td>Lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>
Application of Regulatory Toxicology to Risk Assessment

<table>
<thead>
<tr>
<th>In-life observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic observations</td>
</tr>
<tr>
<td>Pathology</td>
</tr>
<tr>
<td>Clinical chemistry</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Which findings are adverse?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which are relevant for humans?</td>
</tr>
<tr>
<td>What are the consequences for the risk-benefit analysis?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do we progress into humans?</th>
</tr>
</thead>
<tbody>
<tr>
<td>And at what dose?</td>
</tr>
<tr>
<td>What do we monitor?</td>
</tr>
</tbody>
</table>
A reminder! “Pivotal” GLP studies are vital in the FTIH decision

- Preclinical data: critical for the FTIH decision
- Clinical safety data become increasingly important as clinical trials progress
- Human data outrank nonhuman data in assessing human safety!
- The **regulatory submission** evolves to an integrated package of non-clinical and clinical data that assesses risk-benefit in the patient context
Phase I, II and III trials plus marketing authorisation progress based on submission of appropriate regulatory documentation. Data from general toxicology and other studies form these submissions. Well designed, conducted and reported studies $\Rightarrow$ high-quality study summaries, the building blocks of quality submissions. These are assembled into a series of submissions with an executive summary that highlights key toxicological issues. These issues form the basis of the sponsors risk-benefit analysis including proposed starting doses, exposure limits, patient exclusions and clinical monitoring.
Regulatory (Pharmaceutical) Toxicology ensures the safe progression of a drug through testing and into routine clinical practice......

New Drug Application (NDA)  Marketing Authorisation Application (MAA)
Regulatory Toxicology in Other Sectors (with disclaimer as a non-expert!)

Under ICH, generally require equivalence on duration in toxicology studies for human exposure (ICH)
### Table 1

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

<table>
<thead>
<tr>
<th>Maximum Duration of Clinical Trial</th>
<th>Rodents</th>
<th>Non-rodents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2 weeks</td>
<td>2 weeks$^a$</td>
<td>2 weeks$^a$</td>
</tr>
<tr>
<td>Between 2 weeks and 6 months</td>
<td>Same as clinical trial$^b$</td>
<td>Same as clinical trial$^b$</td>
</tr>
<tr>
<td>&gt; 6 months</td>
<td>6 months$^{b,c,e}$</td>
<td>9 months$^{b,c,d}$</td>
</tr>
</tbody>
</table>

### Table 2

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

<table>
<thead>
<tr>
<th>Duration of Indicated Treatment</th>
<th>Rodent</th>
<th>Non-rodent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 2 weeks</td>
<td>1 month</td>
<td>1 month</td>
</tr>
<tr>
<td>&gt;2 weeks to 1 month</td>
<td>3 months</td>
<td>3 months</td>
</tr>
<tr>
<td>&gt;1 month to 3 months</td>
<td>6 months</td>
<td>6 months</td>
</tr>
<tr>
<td>&gt;3 months</td>
<td>6 months$^e$</td>
<td>9 months$^{c,d}$</td>
</tr>
</tbody>
</table>

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ICH M3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorisation for Pharmaceuticals (2009)

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Industrial chemicals: Driven by production volume/import tonnage (ECHA 2014)
1 month required > 10 tonnes/year.
3 months (chronic) > 100 tonnes/year (could be avoided if the NOAEL-90 can be extrapolated from the NOAEL-28)
>12 months may be required for >1000 tonnes/year
Weight of evidence could be sufficient for classification

For agrochemicals (OECD Guidelines):
Assessed stepwise in:
1-month studies, 3-month studies, chronic studies in rodents
Potentially avoided for natural products

Overall, the testing strategy, risk assessment and labelling approaches for drugs, industrial chemicals and agrochemicals are predicated on the assumption that severity of toxicity increases with duration of exposure (Batke et al, 2011).
### All Sectors Use a Stepwise Approach to Tox Testing:

<table>
<thead>
<tr>
<th></th>
<th>Pharma</th>
<th>Chemicals</th>
<th>Agrochemicals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-month studies (28 days)</td>
<td>Phase I</td>
<td>&gt; 10 tonnes/year</td>
<td>Stepwise: “To obtain initial info”</td>
</tr>
<tr>
<td>3-month studies (subchronic)</td>
<td>Phase II</td>
<td>&gt; 100 tonnes/year</td>
<td>Support of exposure: find a NOEL</td>
</tr>
<tr>
<td>&gt; 6 months (Chronic)</td>
<td>Phase III</td>
<td>&gt;1000 tonnes/year</td>
<td>(12 months) “Prolonged/repeated”</td>
</tr>
</tbody>
</table>
Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

Harry Olson,1 Graham Betton,2 Denise Robinson,3 Karluss Thomas,3 Alastair Monro,1 Gerald Kolaja,4 Patrick Lilly,5 James Sanders,6 Glenn Sipes,7 William Bracken,8 Michael Dorato,9 Koen Van Deun,10 Peter Smith,11 Bruno Berger,2 and Allen Heller12

Preclinical (Safety) Toxicology Testing Predicts the Clinical Outcome: Weight of Evidence

Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals

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Peter Smith1 Bruce Berger3 and Allen Heller2

1Pfizer Inc, Groton, Connecticut
2AstraZeneca Pharmaceuticals, Marlborough, England
3Pfizer Inc, Washington, DC, 19609

The Concordance between Nonclinical and Phase I Clinical Cardiovascular Assessment from a Cross-Company Data Sharing Initiative

Lena Sperbert,1 Mike Acasti,2 Mark Bruinink,1 Mike Hergenwal,3 David D. Gallacher,1 Helena Goya,1 Philip Jervis1, Hsing-Chi Lu,1 Derek Lehmann1, Louise Leong1, Nick McMahan1, Andy Mead4, Phil Miliken1, Willi Suter,1 Ardi Tannat1, Kevin Van Ammel1, Hugo M. Vangelge, Rob Wallia3, and Jean-Francuz Valentin1

1AstraZeneca R&D Millwood, Purchase, New York, 10022, Sweden, 2DaiChenopharm, Inc, Fort Pond, West Harwich, MA, 02671, 3Teva Pharmaceuticals, Jerusalem, Israel, 4Bristol-Myers Squibb, Princeton, NJ 08543, USA

Drug Development and Nonclinical to Clinical Translational Databases: Past and Current Efforts

Thomas M. Monaco

1Angion—Comparative Biology and Safety Sciences, Thousand Oaks, California 91360

The Original Article

Potentials and limitations of nonclinical safety assessment for predicting clinical adverse drug reactions: correlation analysis of 142 approved drugs in Japan

Chihito Tanaki1, Takashi Nagayama1, Masamichi Hashiba1, Masato Fujiseki1, Masanori Hama1, Hiroshi Kodama1, Minoru Nakashima1, Kanuki Suzuki1, Yoshihito Tanahashi1, Yumito Ogawa1, Daisaku Yamasaki1, Takaaki Yasuda1, Shigeo Hidaka1, Takako Ohkura111 and Kazutoshi Nakamura11

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<table>
<thead>
<tr>
<th>Drug (date)</th>
<th>Clinical ARs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesinurad (22 Dec 2015) To treat high uric acid levels during gout</td>
<td>headache, influenza, blood creatinine increased, and gastroesophageal reflux disease</td>
</tr>
<tr>
<td>Uptravi (22 Dec 2015) To treat pulmonary arterial hypertension</td>
<td>headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing.</td>
</tr>
<tr>
<td>Bridion (15th Dec 2015) To reverse neuromuscular blockade during surgery</td>
<td>vomiting, pain, nausea, hypotension, and headache</td>
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<tr>
<td>Alecensa (11th Dec 2015) To treat Alk+ lung cancer</td>
<td>diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, urticarial, headache, oropharyngeal pain, asthenia, constipation, nausea</td>
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</tbody>
</table>
### Drug (date)

<table>
<thead>
<tr>
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<td>To treat high uric acid levels during gout</td>
<td>Gi tract and kidney (rodent)</td>
</tr>
<tr>
<td></td>
<td>To treat high uric acid levels during gout</td>
<td>bile duct hyperplasia (nonrodent)</td>
</tr>
<tr>
<td></td>
<td>headache, influenza, blood</td>
<td></td>
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<tr>
<td></td>
<td>creatinine increased, and</td>
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<tr>
<td></td>
<td>gastroesophageal reflux disease</td>
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<td></td>
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<td>Rodent: liver and adrenal gland</td>
</tr>
<tr>
<td></td>
<td>To treat pulmonary arterial hypertension</td>
<td>Nonrodent: Increased ossification, bone marrow fibrosis, intussusception</td>
</tr>
<tr>
<td></td>
<td>headache, diarrhea, jaw pain,</td>
<td></td>
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<tr>
<td></td>
<td>nausea, myalgia, vomiting, pain in</td>
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<td>extremity, and flushing.</td>
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<tr>
<td>Bridion (15th Dec 2015)</td>
<td>To reverse neuromuscular blockade during surgery</td>
<td>Bone and teeth retention</td>
</tr>
<tr>
<td></td>
<td>vomiting, pain, nausea, hypotension, and headache</td>
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<td></td>
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<td>Rodent: Swelling of the nose and paws</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonrodent: Swelling of the face (Chronic active inflammation)</td>
</tr>
<tr>
<td></td>
<td>diarrhea, vomiting, fever, rhinitis,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>anemia, cough, nasopharyngitis, urticarial, headache,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>oropharyngeal pain, asthenia, constipation, nausea</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
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</tr>
</tbody>
</table>
What is the Aim of Preclinical Safety Testing?

Rodent and non-rodent repeat dose toxicology studies are used to support human clinical trials to assess the safety of new drugs and are a regulatory requirement.
In this summary of >600 projects, 27 (82% of 33) projects were stopped after preclinical safety testing due to unacceptable toxicity.

Net attrition across AZ, Lilly, GSK and Pfizer (605 projects).

...so, for many of the most toxic compounds, there are no clinical correlates....
So preclinical studies stop toxic compounds....what else?

‘This (nonclinical) information is helpful for the estimation of a safe starting dose and dose range for the human trials and the identification of parameters for clinical monitoring for potential adverse effects.................the NOAEL gives the most important information.’
The AstraZeneca Oncology Portfolio 2005–2013

- Preclinical toxicity studies stop unsafe projects before they reach the clinic
- Second species is vital for this stop/go decision
- Preclinical studies inform clinical monitoring

With thanks to AstraZeneca, Damian Deavall and Richard Knight
Challenge: The 3Rs

3Rs: principles relating to the ethical use of animals in scientific research (replacement, reduction, refinement)


UK Law:

*Animals (Scientific Procedures) Act 1986*
The 3Rs

- Principles relating to the ethical use of animals in scientific research

http://www.nc3rs.org.uk/the-3rs

- Does not mean reducing animal usage such that endpoints are missed!
Statistics are Vital in Routine and Bespoke Study Design to Ensure Appropriate Power

The Experimental Design Assistant - EDA | NC3Rs
An efficient use of statistics can reduce the number of animals required and maximise the information obtained per experiment. More complex designs for ...
https://www.nc3rs.org.uk/experimental-design-assistant-eda
Two Species?

- A debate is under way of the value of the second species in regulatory decision making
- The 3Rs arguments are compelling, but it’s a complex area
- Data are being gathered by the NC3Rs

<table>
<thead>
<tr>
<th>Clinical decision</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria</td>
<td>Nonrodent</td>
</tr>
<tr>
<td>Starting Dose</td>
<td>Rodent</td>
</tr>
<tr>
<td>Escalation</td>
<td>Nonrodent</td>
</tr>
<tr>
<td>Exposure limits</td>
<td>Nonrodent</td>
</tr>
<tr>
<td>Stopping criteria</td>
<td>Nonrodent</td>
</tr>
<tr>
<td>Clinical monitoring</td>
<td>Nonrodent</td>
</tr>
</tbody>
</table>

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Challenge: Failure!

Lessons learned from the fate of AstraZeneca’s drug pipeline: a five-dimensional framework

*David Cook, Dearg Brown, Robert Alexander, Ruth March, Paul Morgan, Gemma Satterthwaite and Menelas N. Pangalos*
Entry into the crucial preclinical good laboratory practice (GLP) stage of toxicology testing triggers significant R&D investment yet >20% of AstraZeneca’s potential new medicines have been stopped for safety reasons in this GLP phase alone. How could we avoid at least some of these costly failures? An


“...>20% of AstraZeneca’s potential new medicines stopped for safety reasons in the GLP Phase alone”

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Number of CDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>3</td>
</tr>
<tr>
<td>GI</td>
<td>1</td>
</tr>
<tr>
<td>CNS</td>
<td>2</td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
</tr>
<tr>
<td>CV Pathology</td>
<td>5</td>
</tr>
<tr>
<td>CV Function</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
</tr>
<tr>
<td>Muscle</td>
<td>3</td>
</tr>
<tr>
<td>Unexplained deaths</td>
<td>3</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1</td>
</tr>
<tr>
<td>Lenticular</td>
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</tr>
<tr>
<td>Multiple target organs</td>
<td>3</td>
</tr>
<tr>
<td>Reprotox</td>
<td>1</td>
</tr>
<tr>
<td>Testicular</td>
<td>1</td>
</tr>
<tr>
<td>Adrenal</td>
<td>1</td>
</tr>
<tr>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
</tr>
</tbody>
</table>
Earlier Comprehensive Assessment of CV Safety and Extended DRFs.....?

<table>
<thead>
<tr>
<th>Number of CDs</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Hepatic</td>
</tr>
<tr>
<td></td>
<td>GI</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td>4</td>
<td>CV pathology</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td>1</td>
<td>Muscle</td>
</tr>
<tr>
<td></td>
<td>Unexplained deaths</td>
</tr>
<tr>
<td>3</td>
<td>Pancreas</td>
</tr>
<tr>
<td></td>
<td>Thyroid</td>
</tr>
<tr>
<td>2</td>
<td>Lenticular</td>
</tr>
<tr>
<td></td>
<td>Multiple target organ toxicities</td>
</tr>
<tr>
<td></td>
<td>CV function</td>
</tr>
<tr>
<td>24 (50%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CV pathology</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td></td>
<td>Reprotoxicity</td>
</tr>
<tr>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>4</td>
<td>NA</td>
</tr>
<tr>
<td>9 (19%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Renal</td>
</tr>
<tr>
<td>1</td>
<td>Liver</td>
</tr>
<tr>
<td>2</td>
<td>Lung</td>
</tr>
<tr>
<td>1</td>
<td>Muscle</td>
</tr>
<tr>
<td>1</td>
<td>Testicular</td>
</tr>
<tr>
<td>1</td>
<td>Adrenal</td>
</tr>
<tr>
<td>2</td>
<td>Multiple organ toxicities</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>11 (23%)</td>
<td></td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>48 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
Doing more earlier gives an earlier idea of risks…..but with what confidence?
  • Cost of doing more on multiple compounds
  • And are results valuable?
  • The ultimate ‘prediction’ is the GLP tox study (for FTIH)
Risk – Benefit: if we stop all potentially unsafe medicines, we might stop many safe medicines with great patient benefit…..

Attrition: What Would You Do?
Future Perspectives

• Drivers for change
  • 3Rs: Reduce, refine, replace
  • Reduce attrition
  • Improve translation

• Assumptions
  • Need for recovery groups
  • Need for second species
  • Dependency on animal data
Current Status of Decision-Making in Drug Safety Testing

- Animal data only
- In silico/in vitro methods plus ‘for cause’ animal studies
- Animal data plus in silico/in vitro methods
- In silico/in vitro only

Today  2020  2025  2030  2035  2040

Eminent Toxicologist Lecture Series • Society of Toxicology
There may be trouble ahead

All site visitors please note that while there is:

- Moonlight
- Music
- Love
- Romance

It is advised that you:

- Face the music
- Dance

Future of Drug Safety Testing
Towards *In Silico-In Vitro* (ISIV) Replacement of Animal Methods: A European Regulatory Perspective

Eminent Toxicologist Lecture Series • Society of Toxicology
Towards *In Silico-In Vitro* (ISIV) Replacement of Animal Methods: A US Perspective
Practical Considerations: ICH is a Guideline Implemented by National Authorities so Local Practices and Interpretation Can Differ

- CFDA (China)
- USA Regulations
  - Department of Health and Human Services, Food and Drug Administration (FDA), Federal Register
  - FDA Center for Drug Evaluation and Research (CDER)
- Japanese Regulations
  - Ministry of Health, Labour and Welfare (MHLW)
- UK Regulations
  - Medicines and Healthcare products Regulatory Agency (MHRA)
- EU Regulations
  - European Medicines Agency (EMA)
We can Invoke Data and Guidelines, but Judgement and Experience are Key.....
Regulatory Toxicology: Learning Objectives

• Understand the purpose of pharmaceutical toxicology
• Understand the pivotal role played by general toxicology studies in protecting volunteer and patient safety
• Understand common principles with other sectors (Agrochemicals, general chemicals)
• Understand outcome of general toxicology studies and the principles and caveats of their designs
• Understand the global framework provided by ICH
• Understand the scope for scientific interpretation (guideline versus ‘rules’)
• Have a perspective on challenges to the current paradigm
References/Further Reading

• ICH  http://www.ich.org
• ECHA  http://echa.Europa.eu
• OECD  http://www.oecd-ilibrary.org
• FDA  http://FDA.gov
• EMA  www.ema.europa.eu/ema
• JFDA  https://www.pmda.go.jp
• NC3Rs  https://www.nc3rs.org.uk/