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

Society of Toxicology

Conflict of Interest Declaration

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

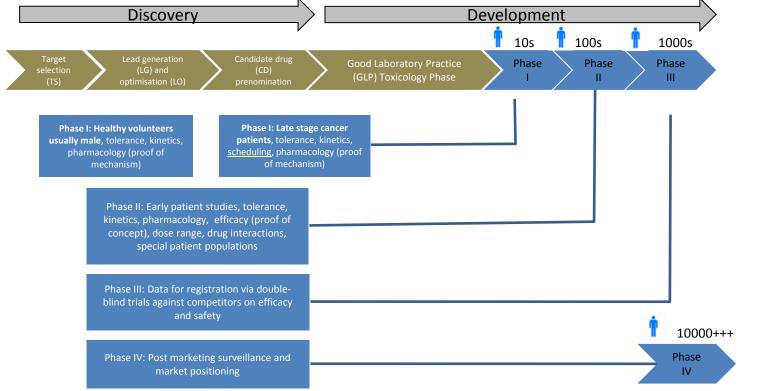
- Outline and purpose of regulatory toxicology testing for pharmaceuticals
 - Overall design of the package from first time in humans (FTIH) through to marketing authorisation
 - Purpose: ensuring volunteer and patient safety in clinical trials
 - Decision making
- General Toxicology
 - Maximum tolerated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

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 the <u>International Council for</u> <u>Harmonisation of Technical Requirements for Pharmaceuticals for Human Use</u> (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



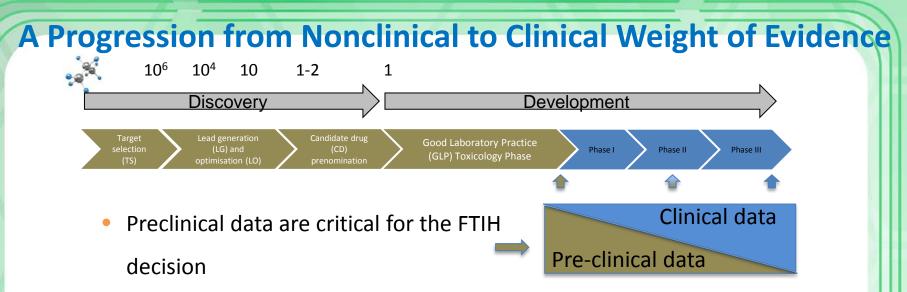


Aim of Preclinical Testing is to Determine Safety Margins

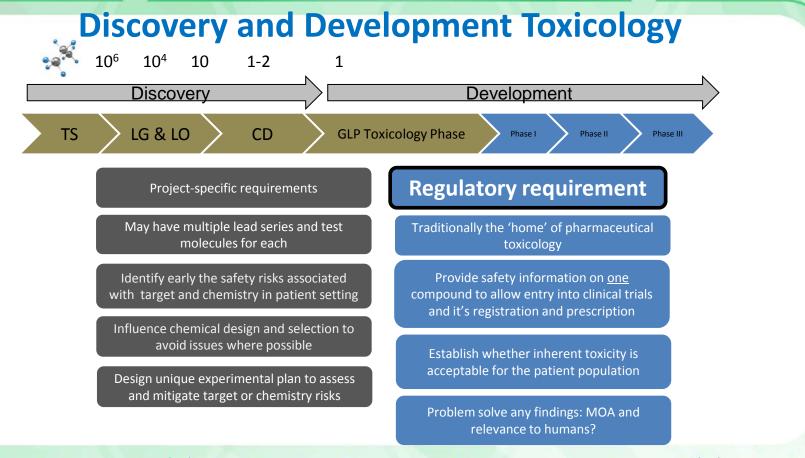


Exposure

For benign indications, 100-fold margin may be appropriate For terminal conditions, much lower margin may be acceptable



- Clinical safety data become increasingly important as clinical trials progress
- Human data outrank nonhuman data in assessing human safety! 1



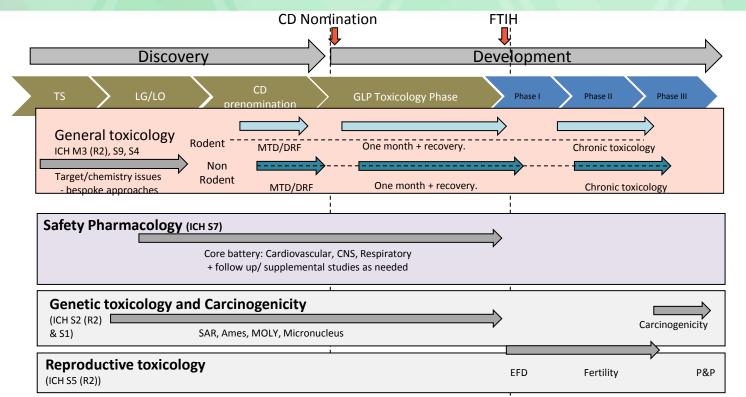
Regulatory Toxicology: What Is It and What's It For?

harmonisation for better health

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'.*

| S1A - S1C Carcinogenicity Studies | 0 |
|--|-------|
| S2 Genotoxicity Studies | • |
| S3A - S3B Toxicokinetics and Pharmacokinetics | • |
| S4 Toxicity Testing | • |
| S5 Reproductive Toxicology | • |
| S6 Biotechnological Products | • |
| S7A - S7B Pharmacology Studies | • |
| S8 Immunotoxicology Studies | • |
| S9 Nonclinical Evaluation for Anticancer Pharmaceuticals | • |
| S10 Photosafety Evaluation | • Etc |
| | |

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,

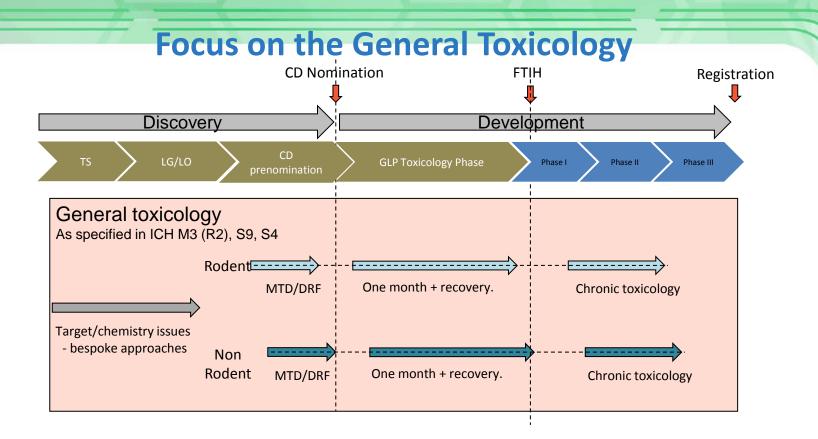
dependency?



Translating Regulatory Guidance into Preclinical Studies: Safety Evaluation of a New Small Molecule

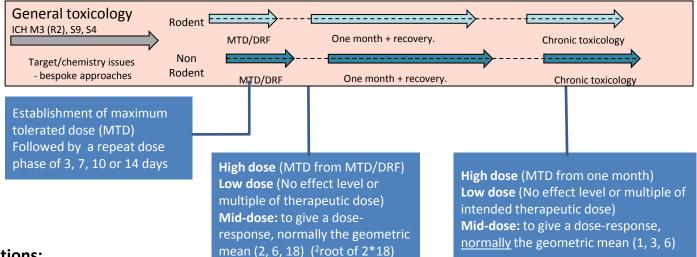
- Formulation
 - stability/homogeneity, etc.
- General Toxicology
 - Acute studies (some countries)
 - Dose Range Finding (DRF) studies
 in rats & dogs
 - 1-month studies in rats & dogs
 - 6-month studies in rats and dogs
 - 9-month/1-year study in dogs
- Oncogenicity
 - sighting study and transgenic 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



MTD/DRF: Maximum tolerated dose/dose range finding

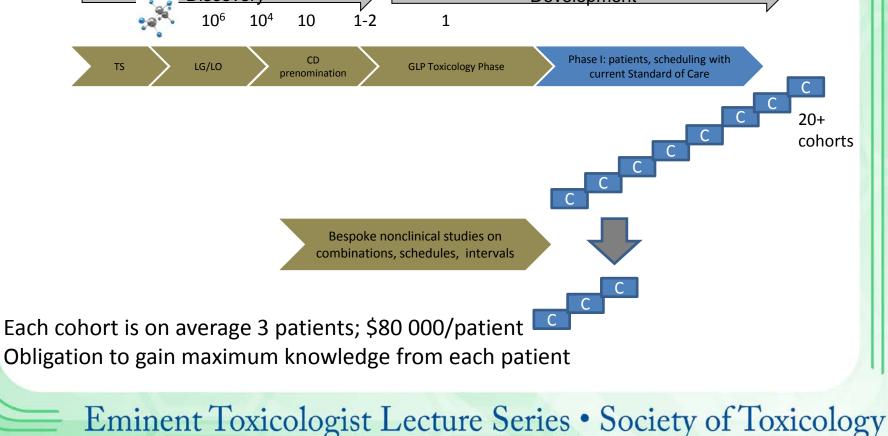
Dose Selection and Progression



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





Species Selection

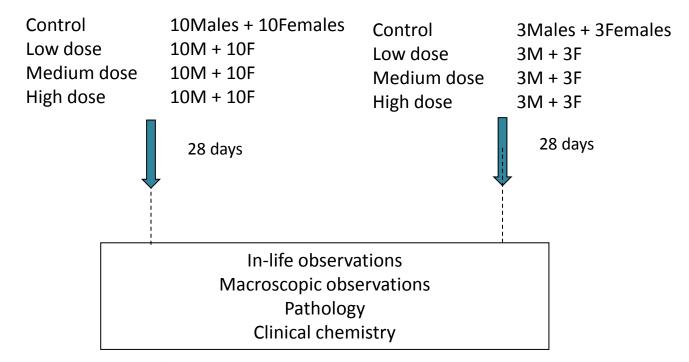
- Two species=regulatory requirement (historically, mainly rat and dog)
- Other species may be used if data suggest they are more appropriate
 - Biological relevance
 - Bioavailability
- Non-human primates or minipigs recognised alternative non-rodent species
- Increasing use of minipigs over dog
- Biotechnology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



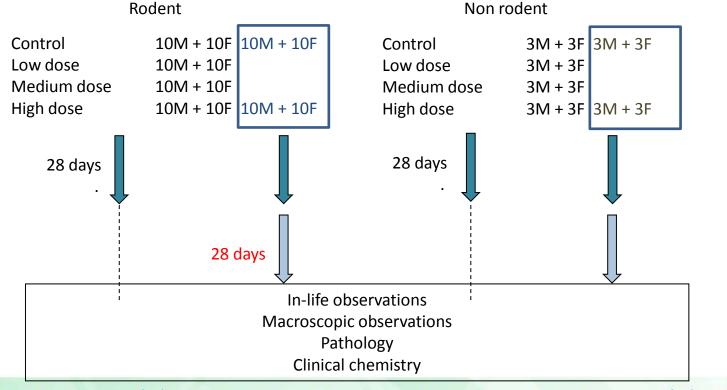
Typical First Time in Humans (FTIH) Study Design

Rodent (n supports statistics)

Non-rodent (no stats)



A Typical FTIH Package also Includes Recovery

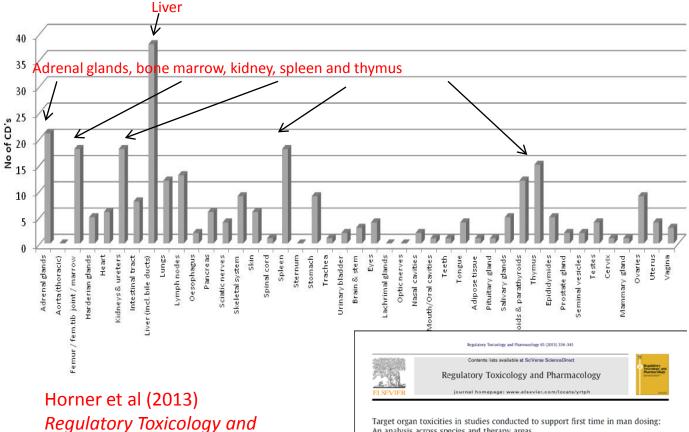


General Toxicology under ICH M3/ICH S9



- 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)

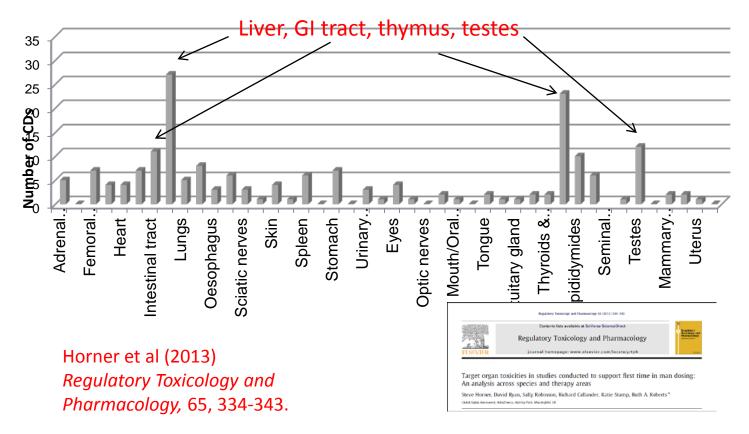


Pharmacology, 65, 334-343.

Steve Horner, David Rvan, Sally Robinson, Richard Callander, Katie Stamp, Ruth A. Roberts* Global Safety Assessment, AstraZeneca, Alderley Park, Macclesfield, U

An analysis across species and therapy areas

FTIM Target Organ Profiles — Non-Rodent (77 studies)



Liver Is the Most Frequent Target Organ in Rodent and Non-Rodent FTIH Studies

| Target Organ | Non-rodent | Rodent |
|--------------|-------------|-------------------|
| 1 | Liver | Liver |
| 2 | Thymus | Adrenal |
| 3 | GI | Spleen Kidneys |
| 4 | Testes | Bone Marrow |
| 5 | Lymph nodes | |

Application of Regulatory Toxicology to Risk Assessment

In-life observations Macroscopic observations Pathology Clinical chemistry

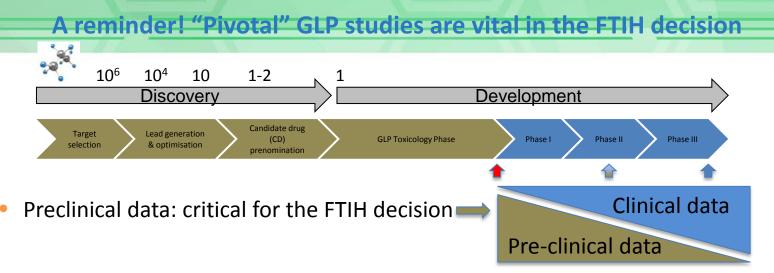
Which findings are adverse?

Which are relevant for humans?

What are the consequences for the risk-benefit analysis?

Do we progress into humans? And at what dose?

What do we monitor?



- 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

A Word on Regulatory Submissions . . .

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 => 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)

Duration of Repeat Dose Toxicology Studies Depends on Clinical Trial Duration

| Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Sup Conduct of Clinical Trials | | |
|--|-------------------------------------|-------------------------------------|
| Maximum Duration of Clinical Trial | I | |
| | Rodents | Non-rodents |
| Up to 2 weeks | 2 weeks ^a | 2 weeks ^a |
| Between 2 weeks and 6 months | Same as clinical trial ^b | Same as clinical trial ^b |
| > 6 months | 6 months ^{b, c} | 9 months ^{b, c, d} |

Table 2 Recommended Duration of Repeated-Dose Toxicity Studies to Support Marketing

| Duration of Indicated | Rodent | Non-rodent | |
|-----------------------|-----------------------|-------------------------|--|
| Treatment | | | |
| 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 ^e | 9 months ^{c,d} | |

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

Regulatory Toxicology in Other Sectors (with disclaimer as a non-expert!)

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):

<u>Assessed stepwise</u> 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:

| | Pharma | Chemicals | Agrochemicals |
|------------------------------------|----------------------------------|-------------------------------|--|
| Guidelines/ standards | ICH <u>http://www.ich.org</u> | ECHA http://echa.Europa.eu | OECD http://www.oecd- ilibrary.org |
| 1-month studies (28 days) | Phase I | > 10 tonnes/year | Stepwise: "To obtain initial info" |
| 3-month studies (subchronic) | Phase II | > 100 tonnes/year | Support of exposure: find a NOEL |
| > 6 months (Chronic) | Phase III | >1000 tonnes/year | (12 months) "Prolonged/repeated" |



Concordance and Translation



Regulatory Toxicology and Pharmacology 32, 56–67 (2000) doi:10.1006/rtph.2000.1399, available online at http://www.idealibrary.com on IDE L

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 Bruce Berger,¹² and Allen Heller¹³

¹Pfizer Inc., Groton, Connecticut; ²AstraZeneca Pharmaceuticals, Macclesfield, England; ³ILSI-HESI, Washington, DC, 20036; ⁴Pharmacia & UpJohn, Kalamazoo, Michigan; ⁶Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut; ¹Rhone-Poulenc Rorer, Collegeville, Pennsylvania; ¹University of Arizona, Tucson, Arizona; ⁸Abbott Laboratories, Abbott Park, Illinois; ⁶Eli Lilly and Co., Greenfield, Indiana; ¹⁰Janssen Research Foundation, Beerse, Belgium; ¹¹Monsanto-Searle Laboratories, Skokie, Illinois; ¹²Sanofi-Synthelabo, Inc., Malvern, Pennsylvania; and ¹³Bayer Corporation, West Haven, Connecticut





Preclinical (Safety) Toxicology Testing Predicts the Clinical

Outcome: Weight of Evidence

Regulatory Toxicology and Pharmacology 32, 56-67 (2000) doi:10.1006/rtph.2000.1399, available online at http://www.idealibrary.com on IDEAL®



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¹Pliner Inc., Gratur, Connecticut; ²AstraZeneca Pharmaceuticals, Macclesheld, England; ³ILSI-HESI, Washington, DC, 20036; ⁴Pharmacia & UpJohn, Kalamaaoo, Michigan, ¹Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut, ⁴Rinne Poulenc Korer, Collegeville, Pennsylvania; ^{*}University of Arizona, Tucson, Arizona; *Abbott Laboratories, Abbott Park, Illinois; *Eli Lilly and Co., Greenfield, Indiana "Janssen Research Foundation, Beerse, Belghum, "Monsanto-Searle Laboratories, Skokle, Illinois, "Sanofi-Synthelaba, Inc., Malvern, Pennsylvania; and "Bayer Corporation, West Haven, Connecticut

Received January 22, 2000

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TOXOCOLOGICAL SCIENCES, 2014, 1-8 dei: 10.1095/terraid \$4:198

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

Lorna Ewart^{1,1}, Mike Aylott^{1,2}, Mark Deurinck², Mike Engwall⁵, David J. Gallacher¹, Helena Geys¹, Philip Jarvis^{1,2}, Haisong Ju¹ Derek Leishman Louise Leong Nick McMahon¹, Andy Mead⁴, Phil Milliken[†], Willi Suter[‡], Ard Teisman[§], Karel Van Ammel[¶], Hugo M. Vargas[§], Rob Wallis^{**}, and Jean-Pierre Valentin^{*,2}

"AstraZeneca R&D Mölndal, Pepparedaieden 1, 431 83, Mölndal, Sweden, "GlanoSmithKline, Park Road, Ware Hertfordshire, SG12 COP, UK, 'Novartis Pharma AG, PO Box, CH-4002, Basel, Switzerland, "Amgen, Inc. One Amore Genter Drive, Thousand Oaks, CA 91323, Manasen Research & Development, a division of Janssen Pharmaceutica NV, Tumhoutseweg 30, B-2340 Boerse, Belgium, ¹Novartis Institutes for RioMedical Research. One Health Flaza, East Hanover, NJ07936. [12] Lilly and company, Indianapolis, IN 46285, 2 Association of the British Pharmaceutical Industry, 105 Victoria Street, London SW1E 6QT, UK, "Prizer Inc., Eastern Point Road, Groton, CT 06340 and "Safety Pharmacology consultant, Sandwich, Kent, UK



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

Chihiro Tamaki12, Takashi Nagayama13, Masamichi Hashiba14, Masato Fujiyoshi1, Masanori Hizue15, Hiroshi Kodaira16, Minoru Nishida17, Kazuhiko Suzuki18, Yoshiharu Takashima1.8, Yamato Ogino1.18, Daisaku Yasugi1.7, Yasuo Yoneta1.11, Shigeru Hisada^{1,12}, Takako Ohkura^{1,13} and Kazuichi Nakamura^{1,14}



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

THOMAS M. MONTICELLO¹

¹Amgen—Comparative Biology and Safety Sciences. Thousand Oaks. California. USA

TOXICOLOGIC PATHOLOGY





Original Article

Clinical Adverse Reactions (ARs) for FDA-Approved Drugs in 2015 (all small molecules)

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

Preclinical Findings Did not Predict these Clinical ARs....

| Drug (date) | Clinical ARs | Nonclinical findings |
|--|---|---|
| Lesinurad (22 Dec 2015) To treat high uric acid levels during gout | headache, influenza, blood creatinine increased, and gastroesophageal reflux disease | GI tract and kidney (rodent) bile duct hyperplasia (nonrodent) |
| Uptravi (22 Dec 2015) To treat pulmonary arterial hypertension | headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. | Rodent: liver and adrenal gland Nonrodent: Increased ossification, bone marrow fibrosis, intussusception |
| Bridion (15 th Dec 2015) To reverse neuromuscular blockade during surgery | vomiting, pain, nausea, hypotension, and headache | Bone and teeth retention |
| Alecensa (11 th Dec 2015) To treat Alk+ lung cancer | diarrhea, vomiting, fever, rhinitis, anemia, cough, nasopharyngitis, urticarial, headache, oropharyngeal pain, asthenia, constipation, nausea | Rodent: Swelling of the nose and paws Nonrodent: Swelling of the face (Chronic active inflammation) |

Not Surprising When Headache is the Most Frequent ARs.....Very Hard to Detect in Preclinical Species.....

| Drug (date) | Clinical ARs | Nonclinical findings |
|--|--|---|
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What is the Aim of Preclinical Safety Testing?

Regulatory Toxicology and Pharmacology 70 (2014) 270-285



Target organ profiles in toxicity studies supporting human dosing: An assessment of recovery and chronic dosing

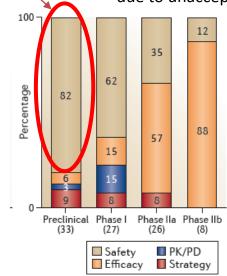


Steve Horner, Sally Robinson, David Lees, Richard Callander, Ruth Roberts*

1. Introduction

Rodent and non-rodent repeat dose toxicology studies are used to support human clinical trials to assess 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....

NATURE REVIEWS DRUG DISCOVERY

VOLUME 13 JUNE 2014 419

So preclinical studies stop toxic compounds....what else?

ICH Topic M 3 (R2) Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals 1.4 General Principles

The development of a pharmaceutical is a stepwise process involving an evaluation of both the animal and human safety information. The goals of the nonclinical safety evaluation generally include a characterisation of toxic effects with respect to target organs, dose dependence, relationship to exposure, and when appropriate, potential reversibility. This information is helpful for the estimation of an initial safe starting dose and dose range for the human trials and the identification of parameters for clinical monitoring for potential adverse effects. The nonclinical safety studies, although limited at the beginning of clinical

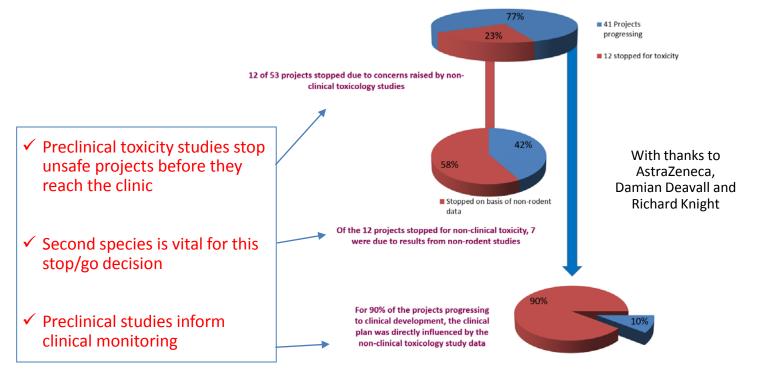
'This (nonclinical) information is helpful for the estimation of a safe starting dose and dose range for the human trials and the identification of parameters for clinical monitoring for potential adverse effects.....the NOAEL gives the most important information.'

U.S. Food and Drug Administration



European Medicines Agency

The AstraZeneca Oncology Portfolio 2005–2013



Challenge: The 3Rs





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



Animals (Scientific Procedures) Act 1986

W.M.S Russell and R.L Burch, 1959, *The Principles* of Humane Experimental Technique, Methuen, London.



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!



Animals (Scientific Procedures) Act 1986

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

| Clinical decision | Species |
|--------------------------|-----------|
| Exclusion criteria | Nonrodent |
| Starting Dose | Rodent |
| Escalation | Nonrodent |
| Exposure limits | Nonrodent |
| Stopping criteria | Nonrodent |
| Clinical monitoring | Nonrodent |

Challenge: Failure!

OUTLOOK

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

NATURE REVIEWS DRUG DISCOVERY

VOLUME 13 JUNE 2014 419

Reducing attrition in drug development: smart loading preclinical safety assessment

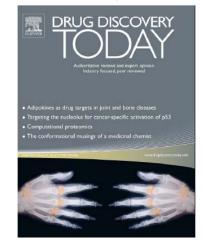
Ruth A. Roberts, Stefan L. Kavanagh, Howard R. Mellor¹, Christopher E. Pollard, Sally Robinson and Stefan J. Platz

Drug Safety and Metabolism, AstraZeneca, Alderley Park, Macclesfield, SK10 4TG, UK

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

Roberts *et al* (2014). Reducing attrition in drug development: smart loading preclinical safety assessment. <u>Drug Discov Today.</u> 2014 Mar;19(3):341-347.

"....>20% of AstraZeneca's potential new medicines stopped for safety reasons in the GLP Phase alone"

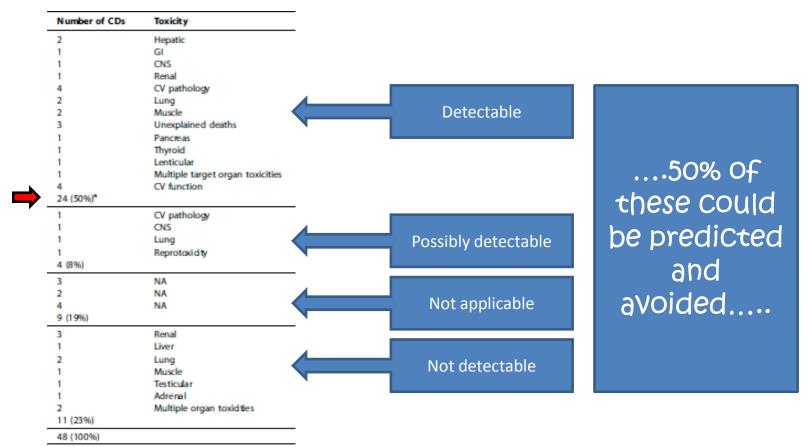


48 AstraZeneca Candidate Drugs that Failed During GLP Tox: Target Organs?

Roberts *et al* (2014). Reducing attrition in drug development: smart loading preclinical safety assessment. <u>Drug Discov Today.</u> 2014 Mar;19(3):341-347.

| Number of CDs |
|---------------|
| 3 |
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| 48 |
| |

Earlier Comprehensive Assessment of CV Safety and Extended DRFs.....?



Attrition: What Would You Do?

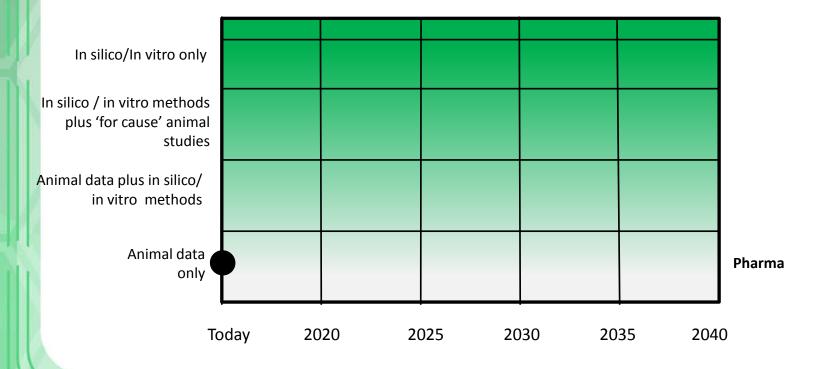
- Doing more earlier gives an earlier idea of risks.....but with what confidence?
 - Cost of doing more on multiple compounds
 - And are results valuable?
 - The ultimate 'prediction' is the GLP tox study (for FTIH)
- Risk Benefit: if we stop all potentially unsafe medicines, we might stop many safe medicines with great patient benefit.....

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



There may be trouble ahead

All site visitors please note that while there is:

Moonlight

Music

Love
 Romance

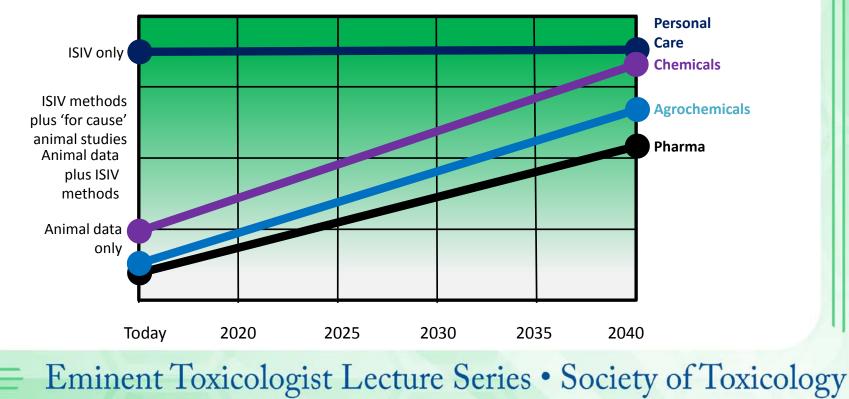
It is advised that you: • Face the music • Dance

Future of

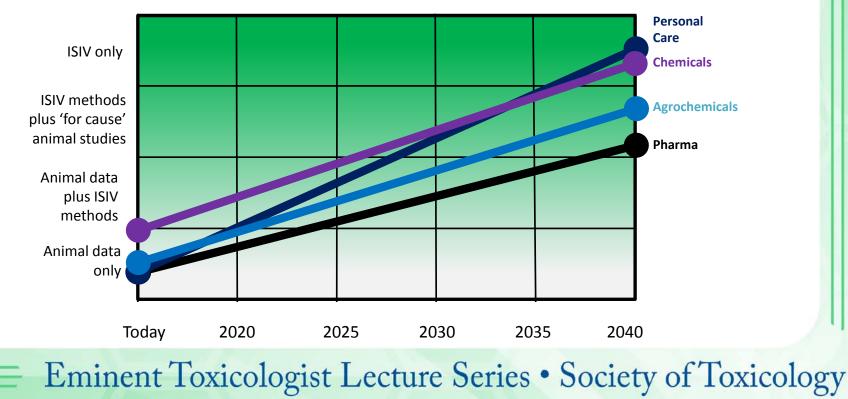
Drug Safety

Testing

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



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

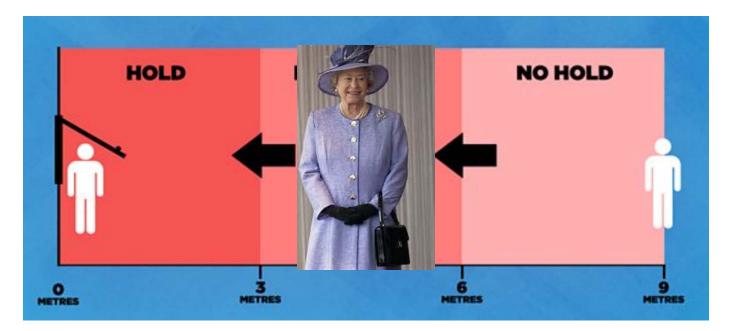
FDA U.S. Food and Drug Administration 🥠 🕬

- 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 <u>http://www.oecd-ilibrary.org</u>
- FDA <u>http://FDA.gov</u>
- EMA <u>www.ema.europa.eu/ema</u>
- JFDA <u>https://www.pmda.go.jp</u>
- NC3Rs <u>https://www.nc3rs.org.uk/</u>