


Regulatory toxicology testing for small molecules: strategies and outcome analysis

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What we will cover today

- ❑ **Context – An overview of regulatory toxicity testing** to support first time in man (FTIM) dosing of small molecules
 - ❑ **Can we reduce time/cost & still ensure human safety?**
 - ❑ FTIM study target organ profiles
 - ❑ Do we need the second species?
 - ❑ Do we need recovery?
 - ❑ **Strategies & recent innovations**
 - ❑ Inclusion of safety pharmacology endpoints in general tox studies
 - ❑ Reducing attrition in the GLP phase of tox testing
- 

WW Regulatory guidelines

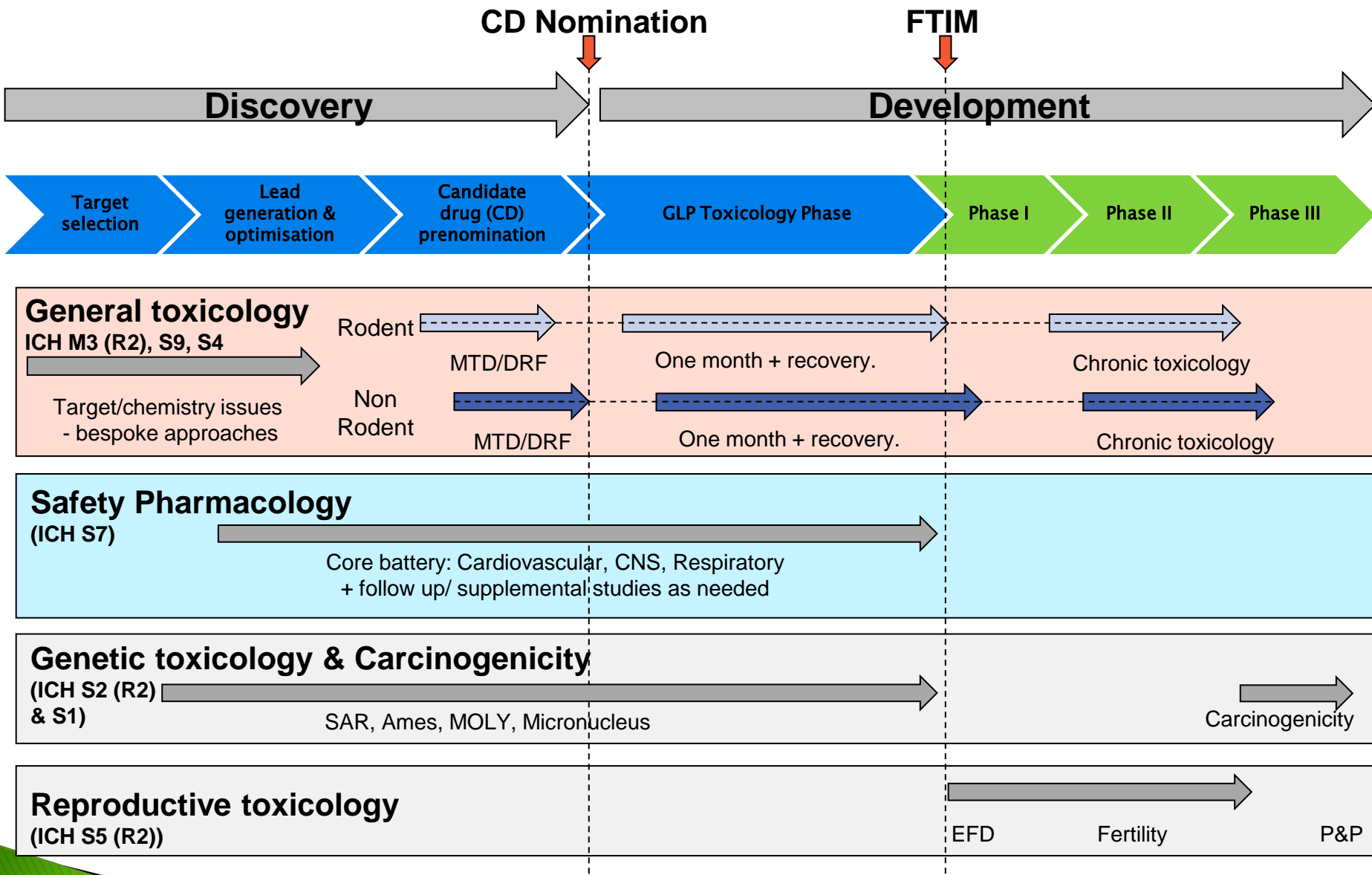


ICH Harmonised Tripartite Guidelines (www.ich.org/products/guidelines.htmlguidelines)

- M3 (R2) GUIDANCE ON **NONCLINICAL SAFETY STUDIES** FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
- S 1A GUIDELINE ON THE NEED FOR **CARCINOGENICITY** STUDIES OF PHARMACEUTICALS
- S 1B TESTING FOR CARCINOGENICITY OF PHARMACEUTICALS
- S 1C DOSE SELECTION FOR CARCINOGENICITY STUDIES OF PHARMACEUTICALS
- S2 (R1) GUIDANCE ON **GENOTOXICITY** TESTING AND DATA INTERPRETATION FOR PHARMACEUTICALS INTENDED FOR HUMAN USE
- S3A NOTE FOR GUIDANCE ON **TOXICOKINETICS**: THE ASSESSMENT OF SYSTEMIC EXPOSURE IN TOXICITY STUDIES
- S3B GUIDANCE FOR REPEATED DOSE TISSUE DISTRIBUTION STUDIES
- S4 DURATION OF **CHRONIC TOXICITY** TESTING IN ANIMALS (RODENT AND NON RODENT TOXICITY TESTING)
- S5 (R2) DETECTION OF TOXICITY TO **REPRODUCTION** FOR MEDICINAL PRODUCTS & TOXICITY TO MALE FERTILITY
- S6 (R1) PRECLINICAL SAFETY EVALUATION OF **BIOTECHNOLOGY**-DERIVED PHARMACEUTICALS
- S7A **SAFETY PHARMACOLOGY** STUDIES FOR HUMAN PHARMACEUTICALS
- S7B THE NON-CLINICAL EVALUATION OF THE POTENTIAL FOR DELAYED VENTRICULAR REPOLARIZATION (QT INTERVAL PROLONGATION) BY HUMAN PHARMACEUTICALS
- S8 **IMMUNOTOXICITY** STUDIES FOR HUMAN PHARMACEUTICALS
- S9 NONCLINICAL EVALUATION FOR **ANTICANCER** PHARMACEUTICALS
- S10 **PHOTOSAFETY** EVALUATION OF PHARMACEUTICALS

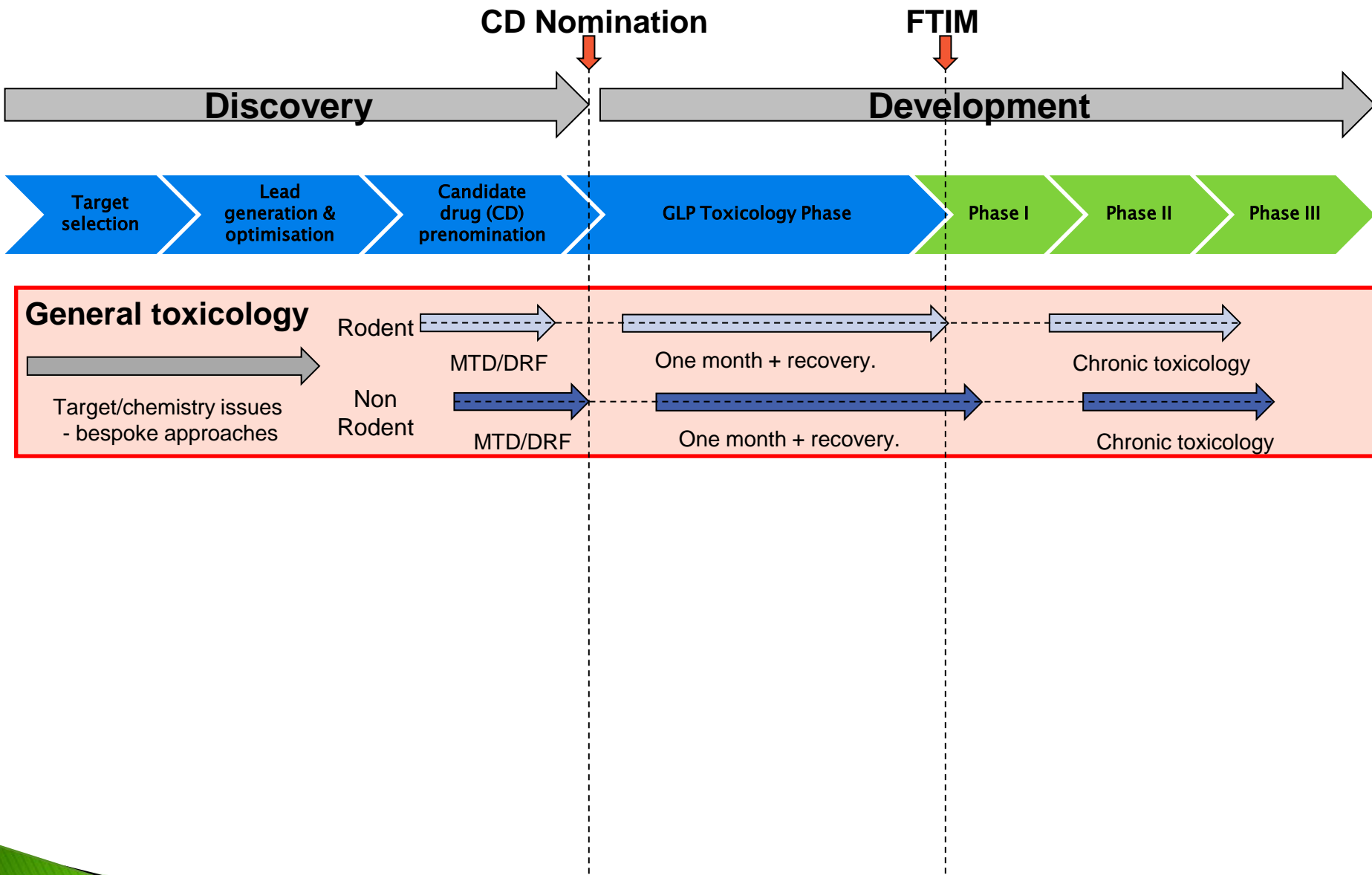


Regulatory toxicology testing for small molecules: an overview



Abbs: CD: candidate drug; FTIM: first time in man; MTD: maximum tolerated dose; DRF: dose range finding; CNS: central nervous system; SAR: structure activity relationship; MOLY: mouse lymphoma assay; EFD: embryofetal development; P&P: peri- and post-natal

Regulatory toxicology testing for small molecules: **general toxicology**



Abbreviations: CD: candidate drug; MTD: maximum tolerated dose; DRF: dose range finding; CNS: central nervous system; SAR: structure activity relationship; MOLY: mouse lymphoma assay; EFD: embryofetal development; P&P: peri- and post-natal

Regulatory toxicology testing for small molecules: assessing risk

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?

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 - ❑ Do we need the second species?
 - ❑ Do we need recovery?

 - ❑ **Strategies & recent innovations**
 - ❑ Inclusion of safety pharmacology endpoints in general tox studies
 - ❑ Reducing attrition in the GLP phase of tox testing
- 

Analysis

- 77 AstraZeneca candidate drugs (CDs)
- Range of therapeutic areas
 - Cardiovascular/GI (16 CDs)
 - CNS/Pain (26 CDs)
 - Respiratory/inflammation (19 CDs)
 - Oncology/Infection (16 CDs)
- Includes CDs that went into humans and those that did not



- Target organ toxicity analyzed, defined as compound-related histopathological changes
- The central nervous system was identified as a target organ if notable in-life observations

Typical FTIM study design

Rodent

Non rodent

Control	10M + 10F
Low dose	10M + 10F
Medium dose	10M + 10F
High dose	10M + 10F

Control	3M + 3F
Low dose	3M + 3F
Medium dose	3M + 3F
High dose	3M + 3F

28 days

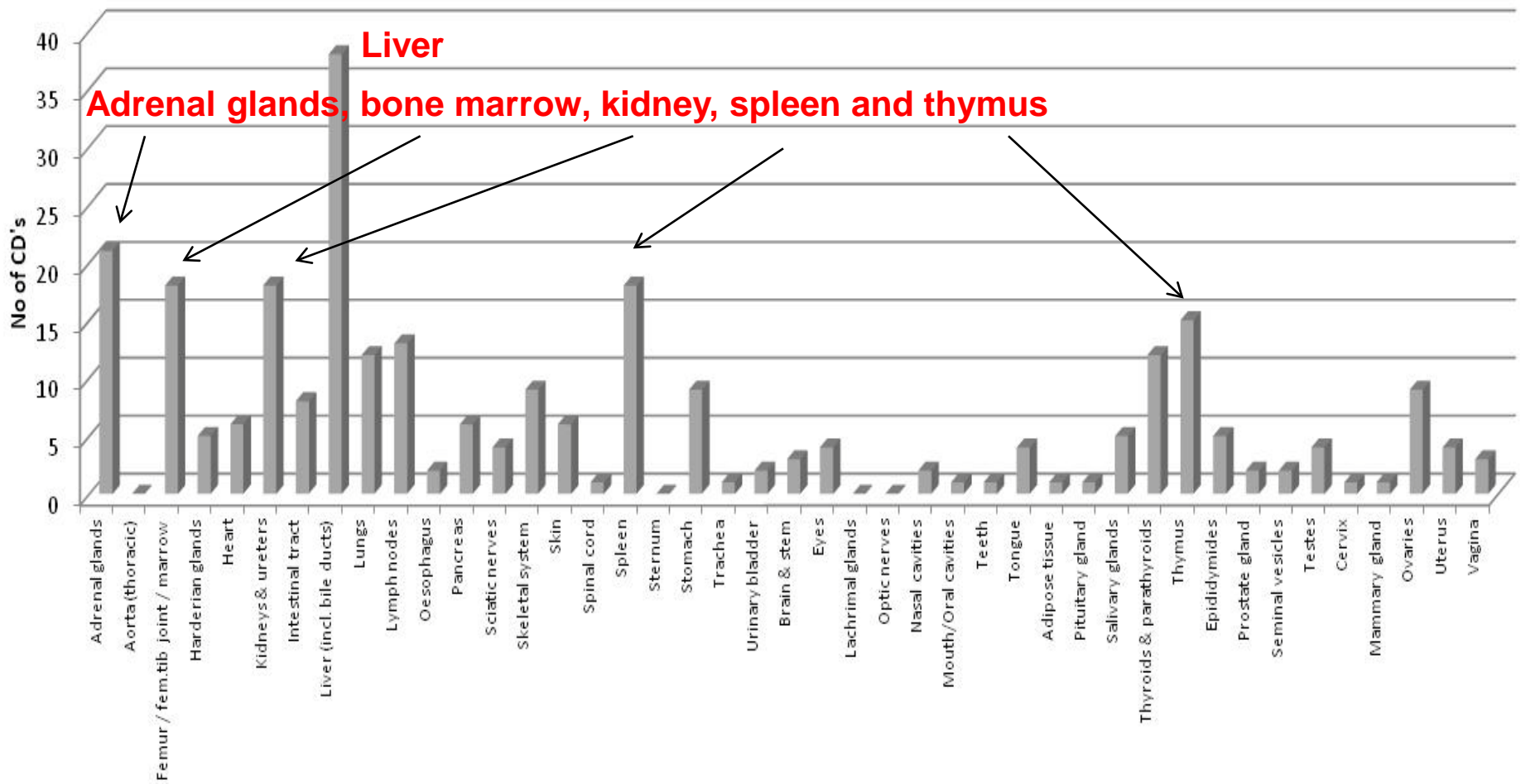


28 days

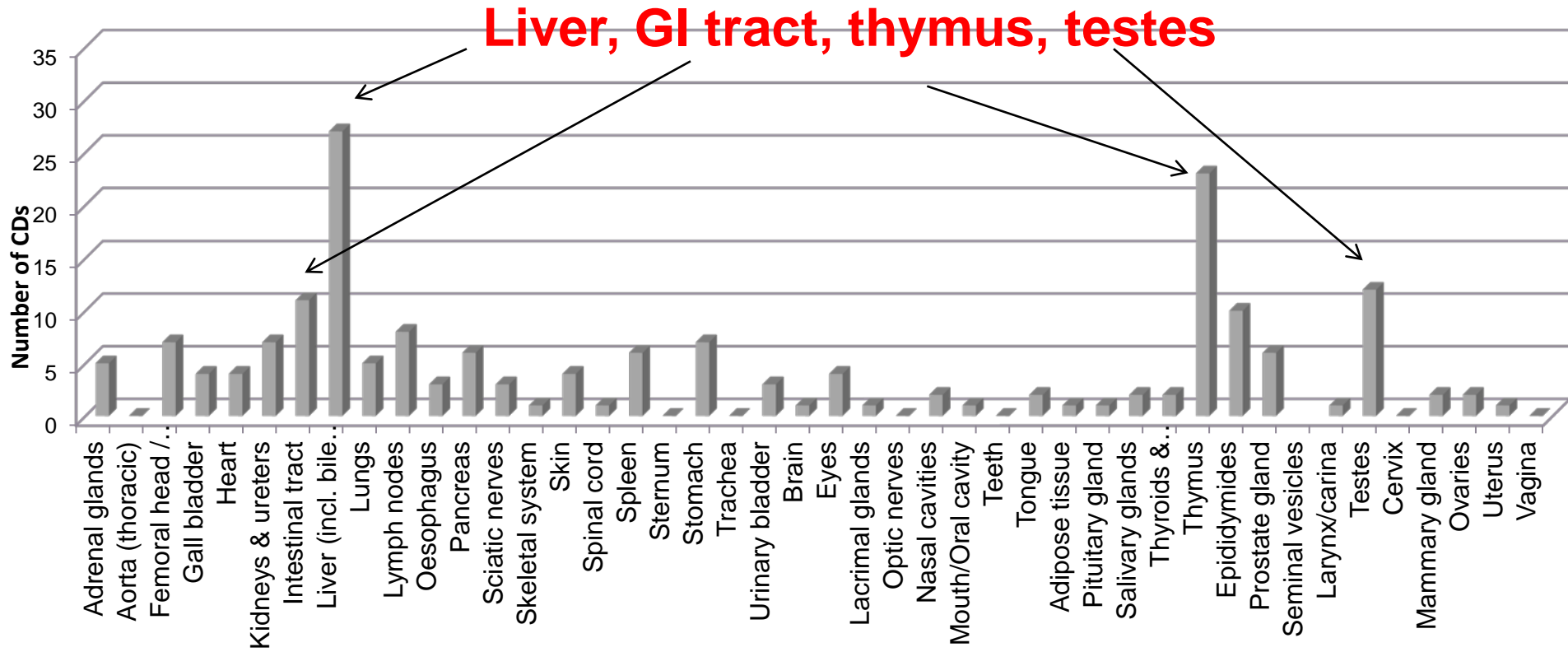


In life observations
Macroscopic observations
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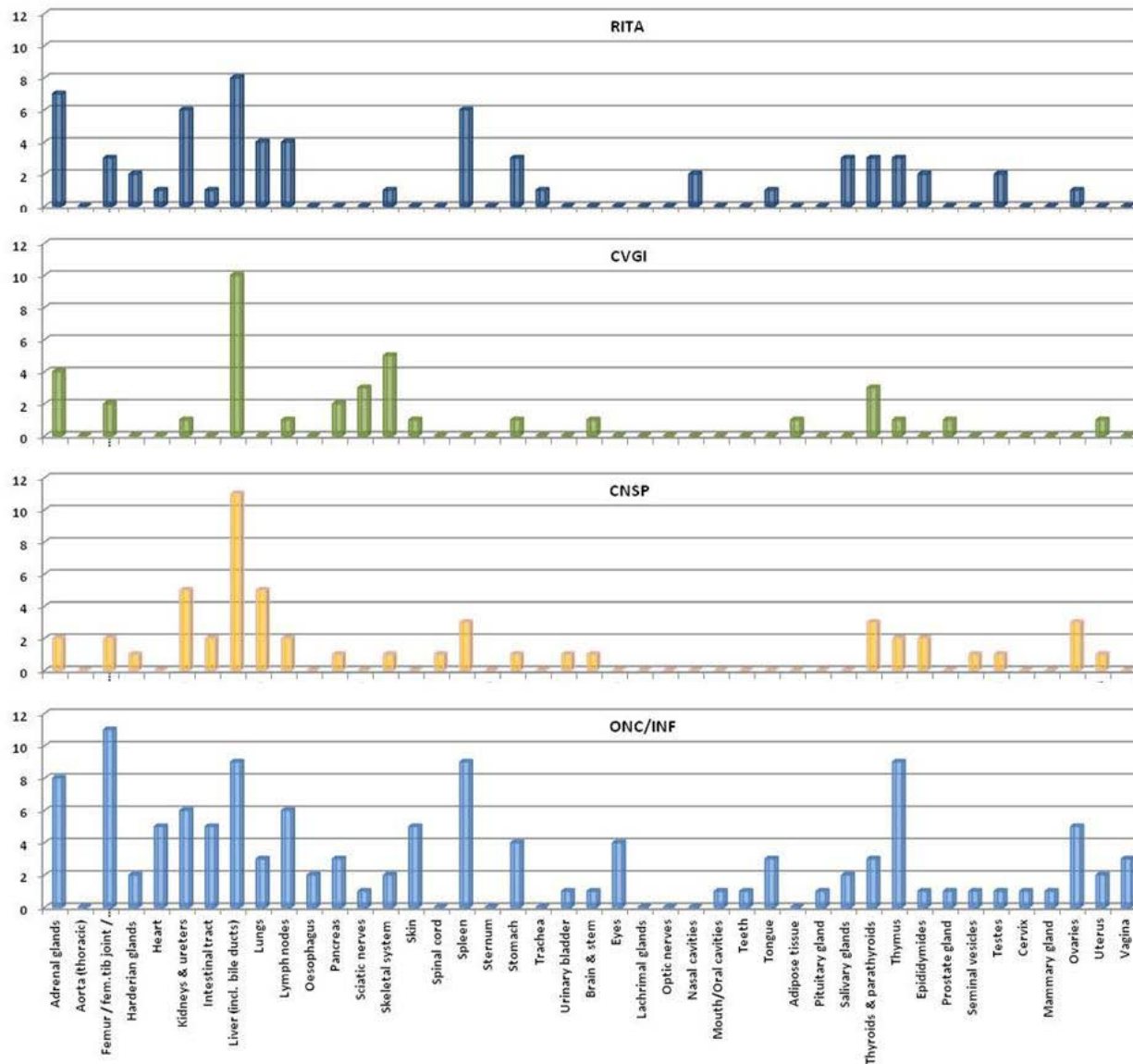
Target organ profiles – rodent (78 studies)



Target organ profiles – nonrodent (77 studies)



Breakdown of target organs identified in 1 month studies for rodents across four therapeutic areas RITA : CVGI: CNSP: OI



Results:

- Profile of target organs affected were similar across therapy areas
- Oncology/infection area differed with a larger range of organs affected
- Profiles were similar for compounds that progressed into man versus those that didn't – decision to progress is multifaceted

Regulatory Toxicology and Pharmacology 65 (2013) 334–343

Contents lists available at SciVerse ScienceDirect

 **Regulatory Toxicology and Pharmacology** 

journal homepage: www.elsevier.com/locate/yrtph

Target organ toxicities in studies conducted to support first time in man dosing:
An analysis across species and therapy areas

Steve Horner, David Ryan, Sally Robinson, Richard Callander, Katie Stamp, Ruth A. Roberts^{*}

Global Safety Assessment, AstraZeneca, Alderley Park, Macclesfield, UK

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An Analysis of the Use of Dogs in Predicting Human Toxicology and Drug Safety

Jarrold Bailey,¹ Michelle Thew¹ and Michael Balls²

Summary — Dogs remain the main non-rodent species in preclinical drug development. Despite the current dearth of new drug approvals and meagre pipelines, this continues, with little supportive evidence of its value or necessity.

What does non rodent add?

Rodent

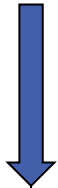


Non rodent

Control	10M + 10F
Low dose	10M + 10F
Medium dose	10M + 10F
High dose	10M + 10F

Control	3M + 3F
Low dose	3M + 3F
Medium dose	3M + 3F
High dose	3M + 3F

28 days



28 days



In life observations
Macroscopic observations
Pathology
Clinical chemistry

New Target Organs were Identified in non-rodents for 43 CDs

Target Organ	Total CDs with unique target organs		Total CDs with common target organs
	NonRodent	Rodent	NonRodent + Rodent
Liver (incl. bile ducts)	9	21	16
Thymus	18	10	5
GI tract/Stomach/Oesophagus	10	8	7
Adrenal glands	2	19	2
Spleen	4	16	2
Femur / fem.tib joint / marrow	2	13	5
Kidneys & ureters	3	14	4
Testis/Epididymis/Prostate/Seminal Vesicle	11	5	2
Lymph nodes	3	7	6
Lungs	3	10	2
Thyroids & parathyroids	0	10	2
Ovary/Uterus/Cervix/Vagina	1	9	1
Heart	3	6	0
Pancreas	3	4	2
Skeletal muscle	0	8	1
Skin	3	4	2
Harderian glands	3	5	0
Mouth/Oral cavity/Teeth/Tongue	2	5	1
Sciatic nerve/Brain/Spinal cord	0	3	4
CNS*	6	1	0
Eyes (+optic nerves)	3	3	1
Salivary glands	2	5	0
Urinary bladder	3	2	0
Mammary gland	2	1	0
Nasal cavities	0	0	2
Pituitary gland	1	1	0
Trachea	0	1	0
Lachrymal glands	1	0	0
Adipose tissue	0	0	1
Total number of CDs with new findings	43# / 75	53 / 75	34 / 75


- For the 75 CDs for which both rodent and non-rodent studies were conducted, new target organs were identified in non-rodents for **43** of the CDs.
- Notably, the changes seen only in non-rodents included organ systems of high relevance for human risk assessment such as **liver, male reproductive tissues & CNS**

First set of conclusions:

- ❑ The data provide **new insights** into drug toxicity profiles in pre-clinical species
- ❑ **Non-rodents** provide key data to support human safety assessment
- ❑ **Risk assessment** depends on defining toxicities and assessing relevance for humans in the context of the **overall risk-benefit**
- ❑ **Broader considerations** such as commercial environment, patent life, size of unmet medical need

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- 

Typical FTIM package includes recovery

Rodent

Non rodent

Control
Low dose
Medium dose
High dose

10M + 10F
10M + 10F
10M + 10F
10M + 10F

10M + 10F
10M + 10F
10M + 10F
10M + 10F

Control
Low dose
Medium dose
High dose

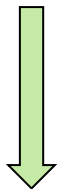
3M + 3F
3M + 3F
3M + 3F
3M + 3F

3M + 3F
3M + 3F
3M + 3F
3M + 3F

28 days



28 days



28 days



28 days



In life observations
Macroscopic observations
Pathology
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Reducing the use of recovery animals in pharmaceutical development



National Centre
for the Replacement
Refinement & Reduction
of Animals in Research

NC3Rs, 2012: National Centre for the Replacement, Refinement & Reduction of Animals in Research, 2012. Reducing the use of recovery animals in pharmaceutical development.

<http://www.nc3rs.org.uk/news.asp?id=1814>



Regulatory Toxicology and Pharmacology

Volume 70, Issue 1, October 2014, Pages 413–429



Sewell, F, Chapman V et al (2014)

Recommendations from a global cross-company data sharing initiative
on the incorporation of recovery phase animals in safety assessment
studies to support first-in-human clinical trials

“Recovery animals should only be included for scientific reasons and not as a default study design”.

Recovery from target organ toxicity is routinely included in FTIM & chronic studies

❑ Is this appropriate?

❑ Can we streamline current practices without compromising patient and volunteer safety?

In life observations
Macroscopic observations
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Clinical chemistry

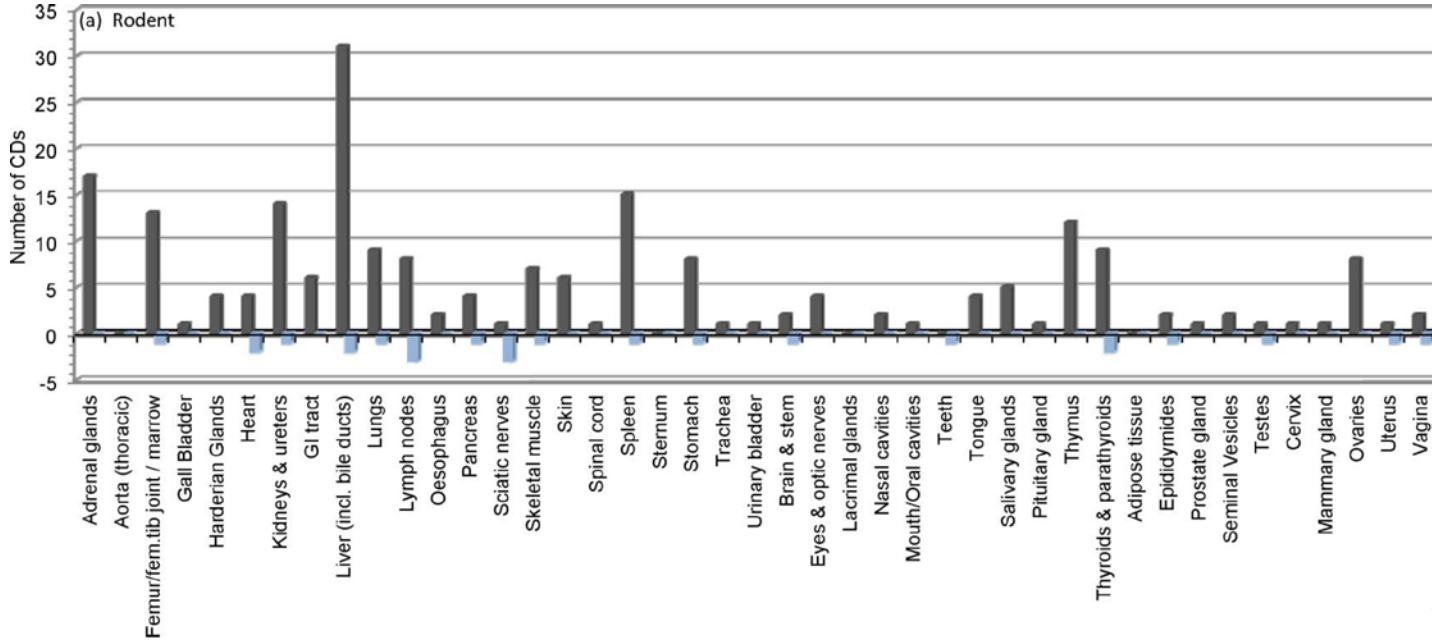


→ Which findings are adverse?
→ Which are relevant for humans?
What are the consequences for the risk-benefit analysis?

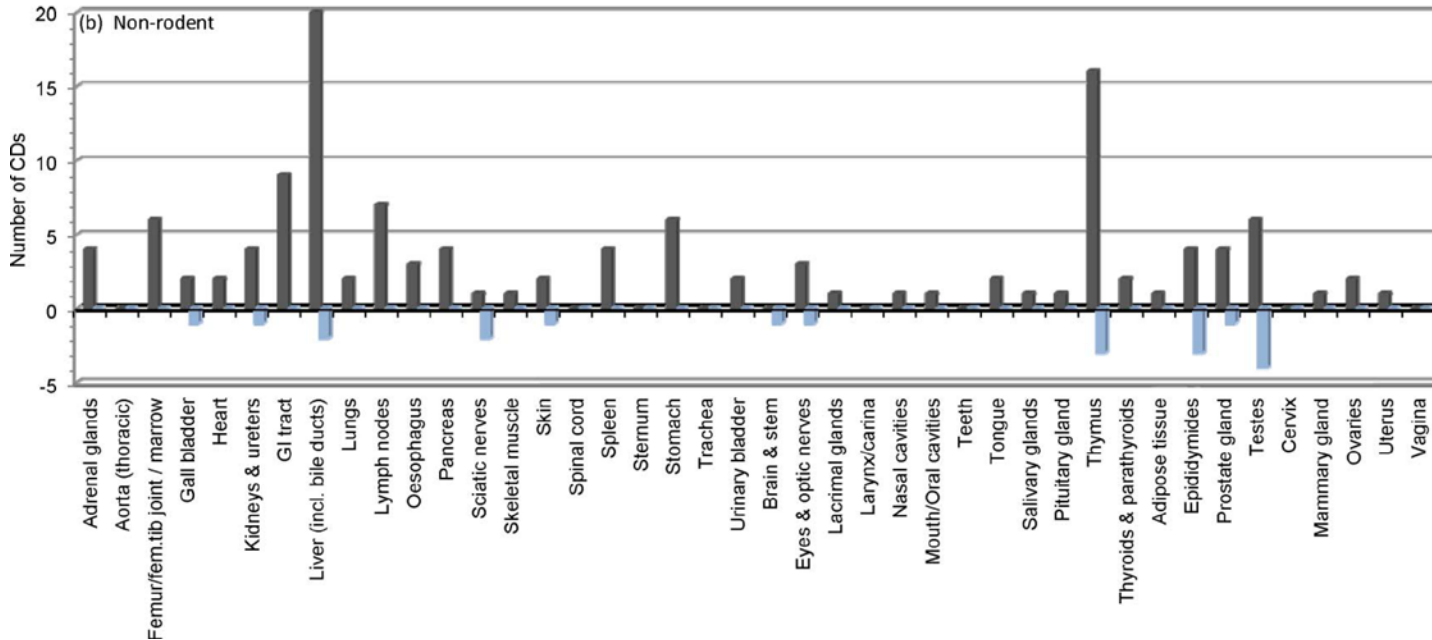


Do we progress into humans?
And at what dose?
What do we monitor?

Analysis of recovery - 54 AstraZeneca Candidate Drugs (CDs)



No of CDs showing toxicity in this organ after 28 days of dosing



No of CDs showing toxicity in this organ after 28 days recovery

	Number of CDs			
	Rodent		Non-rodent	
	Full/Partial recovery	No evidence of recovery	Full/Partial recovery	No evidence of recovery
Liver (incl. bile ducts)	31	2	20	2
Thymus	12	0	16	3
Adrenal glands	17	0	4	0
Spleen	15	1	4	0
Kidneys & ureters	14	1	4	1
Femur / fem.tib joint / marrow	13	1	6	0
Lymph nodes	8	3	7	0
Stomach	8	1	6	0
Gastrointestinal tract	6	0	9	0
Thyroids & parathyroids	9	2	2	0
Epididymides	2	1	4	3
Lungs	9	1	2	0
Testes	1	1	6	4
Ovaries	8	0	2	0
Heart	4	2	2	0
Skeletal muscle	7	1	1	0
Pancreas	4	1	4	0
Skin	6	0	2	1
Eyes (+optic nerves)	4	0	3	1
Prostate gland	1	0	4	1
Salivary glands	5	0	1	0
Tongue	4	0	2	0
Gall bladder	1	0	2	1
Harderian glands	4	0	-	-
Oesophagus	2	0	3	0
Sciatic nerves	1	3	1	2
Brain & stem	2	1	0	1
Urinary bladder	1	0	2	0
Uterus	1	1	1	0
Vagina	2	1	0	0
Mammary gland	1	0	1	0
Nasal cavities	2	0	1	0
Pituitary gland	1	0	1	0
Seminal vesicles	2	0	-	-
Adipose tissue	0	0	1	0
Cervix	1	0	0	0
Lachrimal glands	0	0	1	0
Mouth/Oral cavities	1	0	1	0
Spinal cord	1	0	0	0
Teeth	0	1	0	0
Trachea	1	0	0	0
Aorta	0	0	0	0
Larynx/carina	-	-	0	0
Sternum	0	0	0	0
Total number of Tos	212	25	126	20
% of TO toxicities showing evidence of recovery	89%		86%	

89% (rodent) and 86% (non-rodent) of the target organ toxicities recover

Dog male reproductive tract was the most frequent finding (4/10)

Rat sciatic nerve was the lowest % recovery (1/4)

Lymph nodes showed low recovery in the rodent (3/11) but 100% recovery in the non-rodent

Analysis of recovery for 54 AstraZeneca Candidate Drugs (CDs)

Regulatory Toxicology and Pharmacology 70 (2014) 270–285



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Contents lists available at [ScienceDirect](#)

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



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 *

Drug Safety and Metabolism, AstraZeneca, Alderley Park, Macclesfield, UK

- >85% of findings recover after one month off-dose
- non-recovery could largely be explained by the nature of the lesion or by the relatively short recovery period
- So do we need to include recovery?

Recovery: what do the guidelines say?

ICH Guideline M3(R2), 2009. 'Guidance on nonclinical safety studies for the conduct of human clinical trials....'. www.ich.org

'Reversibility should be assessed when appropriate'

ICH Guideline S9, 2009 'Nonclinical evaluation for anticancer pharmaceuticals.' www.ich.org

'A study that includes a terminal non-dosing period is called for if there is severe toxicity at approximate clinical exposure and recovery cannot be predicted by scientific assessment'



July 2008
CPMP/ICH/286/95

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



U.S. Food and Drug Administration



Assessment of recovery from pharmacological and toxicological effects....

ICH Guideline M3(R2), 2009. 'Guidance on nonclinical safety studies for the conduct of human clinical trials....'. www.ich.org

'Reversibility should be assessed when appropriate'

ICH Guideline S9, 2009 'Nonclinical evaluation for anticancer pharmaceuticals.' www.ich.org

'A study that includes a terminal non-dosing period is called for if there is severe toxicity at approximate clinical exposure and recovery cannot be predicted by scientific assessment'

**ICH M3 (R2) (2011) Questions and Answers document www.ich.org
Scientific assessment could be based on *'the extent and severity of the lesion, the regenerative capacity of the organ and knowledge of other drugs causing the effect'*.**

**But the site and severity of the lesion
is not normally known.....**

A proposal - points to be considered when site and severity of the lesions and hence whether they can be predicted to recover is not yet known:

1. Target effects – from published literature or previous practical experience
2. Chemistry (or related chemistry) effects – from structural data bases or prior experience
3. Prior in vivo experience - data obtained from earlier work such as dose range finding, efficacy or DMPK studies

Regulatory Toxicology and Pharmacology 70 (2014) 572–573



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Letter to the Editor

What constitutes scientific justification for inclusion of recovery assessment in pre-clinical studies supporting first time in man (FTIM)?

Sally Robinson
Ruth Roberts*
UK

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Response from MHRA...

Regulatory Toxicology and Pharmacology 70 (2014) 574



Contents lists available at [ScienceDirect](#)

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph



Letter to the Editor

Response to “What constitutes scientific justification for inclusion of recovery assessment in pre-clinical studies supporting first time in man (FTIM)?” Sally Robinson and Ruth Roberts, Drug Safety and Metabolism, AstraZeneca, Alderley Park, Macclesfield, UK

I fully agree with Sally and Ruth's conclusion that recovery should not routinely be included in the pivotal good laboratory practise (GLP) compliant non-clinical studies supporting FTIM, and this was also the conclusion of the NC3Rs/MHRA group.

References

- Working to reduce the use of animals in scientific research. Crown copyright 2014. ISBN 978-1-78246-264-4.
- NC3Rs (National Centre for the Replacement, Refinement & Reduction of Animals in Research), 2012. Reducing the use of recovery animals in pharmaceutical development. <<http://www.nc3rs.org.uk/news.asp?id=1814>>.

David R. Jones
Expert Pharmacotoxicologist
MHRA, United Kingdom

Removal of the need for acute toxicity testing is a good example of where international guidelines have changed driven by an integrated, global, evidence-based consensus lead by industry.

Regul Toxicol Pharmacol. 2008 Apr;50(3):345-52. doi: 10.1016/j.yrtph.2007.11.009. Epub 2007 Dec 5.

A European pharmaceutical company initiative challenging the regulatory requirement for acute toxicity studies in pharmaceutical drug development.

Robinson S¹, Delongueas JL, Donald E, Dreher D, Festag M, Kervyn S, Lampo A, Nahas K, Noques V, Ockert D, Quinn K, Old S, Pickersquill N, Somers K, Stark C, Stei P, Waterson L, Chapman K.



European Medicines Agency

July 2008
CPMP/ICH/286/95

**ICH Topic M3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals**

Second set of conclusions:

- ❑ **Non-rodents** provide key data to support human safety assessment
- ❑ **Move away from inclusion of recovery on the FTIM studies as default**

Recovery assessment in pre-clinical drug safety testing – a retrospective analysis of impact and timing

[Regulatory Toxicology and Pharmacology 70 \(2014\) 270-285](#)

Sally Robinson, Steve Horner, David Lees, Richard Callander & Ruth Roberts
Drug Safety and Metabolism, AstraZeneca, Alderley Park, Macclesfield, UK

What constitutes scientific justification for inclusion of recovery assessment in pre-clinical studies supporting first time in man (FTIM)?

[Regulatory Toxicology and Pharmacology 70 \(2014\) 572-573.](#)

Sally Robinson & Ruth Roberts

Regulatory Toxicology and Pharmacology 65 (2013) 334-343

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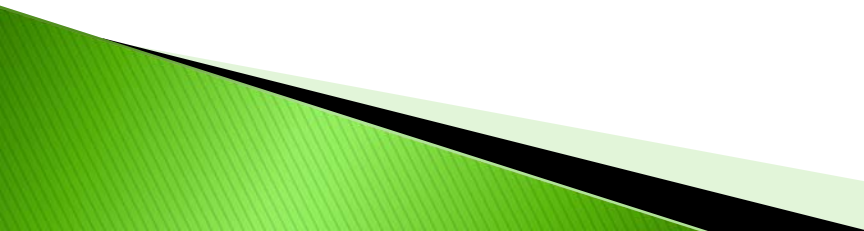


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Functional assessments in repeat-dose toxicity studies: the art of the possible

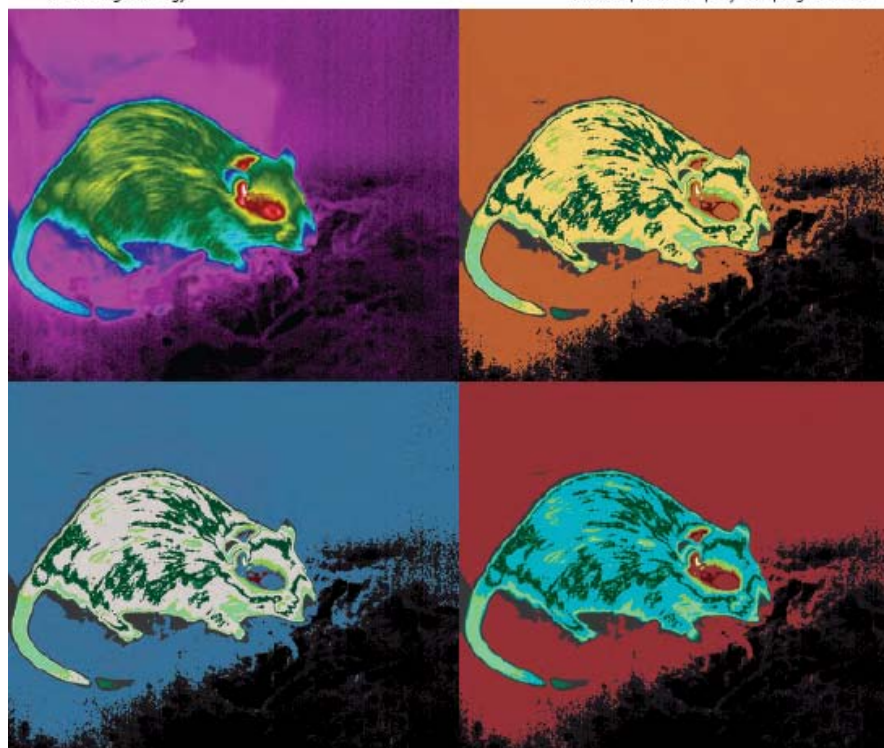
Will S. Redfern,* Lorna C. Ewart, Pierre Lainée,† Mark Pinches, Sally Robinson and
Jean-Pierre Valentin

Toxicology Research

www.zsc.org/toxicology

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Functional assessments in repeat-dose toxicity studies: the art of the possible

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Will S. Redfern,* Lorna C. Ewart, Pierre Lainée,† Mark Pinches, Sally Robinson and Jean-Pierre Valentin

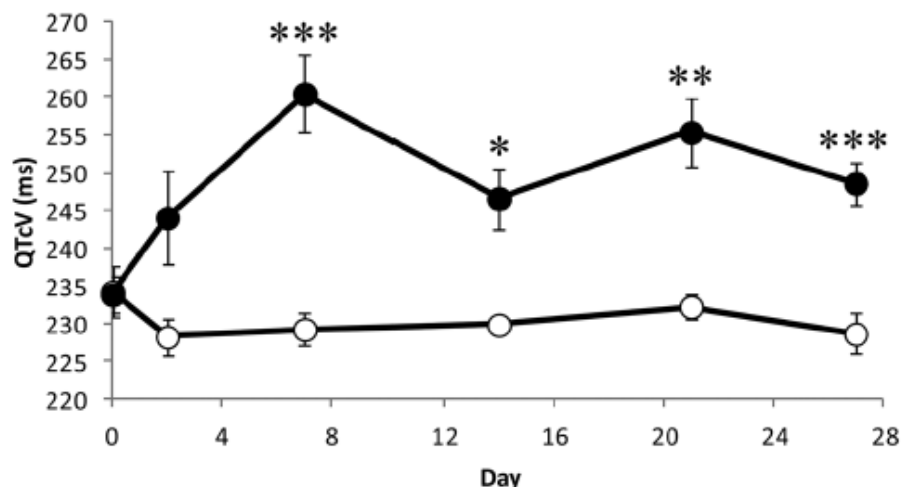


Fig. 2 Example of drug-induced QTc prolongation during a 28-day toxicology study in beagle dogs. ECGs were recording in freely moving dogs using a non-invasive telemetry system. Open symbols: vehicle-treated, $n = 5$; filled symbols: compound-treated group, $n = 4-6$. Note the overall stability of QTc over the one-month recording period in the vehicle control group. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs. vehicle control group. (In-house data.)

QTc prolongation

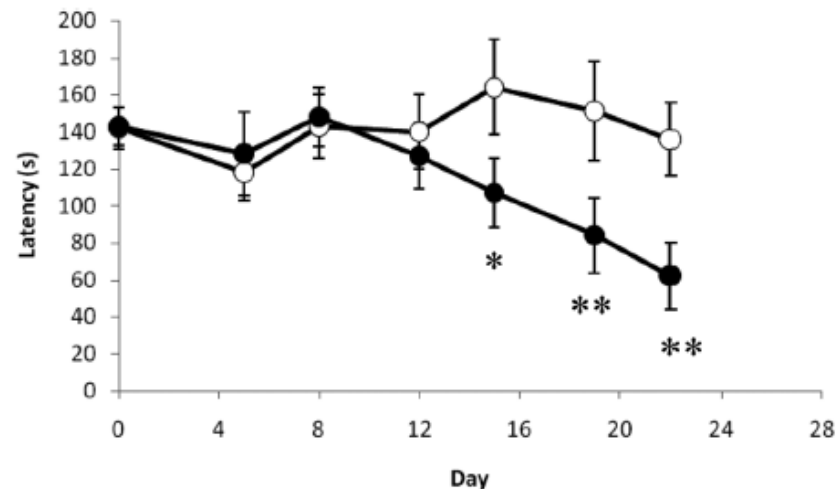


Fig. 3 Deterioration of performance in rats in an accelerating rotarod task during repeated dosing of a compound associated with skeletal muscle toxicity. Open symbols: vehicle-treated, $n = 10$; filled symbols: compound-treated group, $n = 10$. A deficit in rotarod performance was detected before the appearance of clinical signs. It also mirrored the development of pathology. * $P < 0.05$; ** $P < 0.01$ vs. vehicle control group. (In-house data.)

Rotarod task deterioration

Redfern et al 2013: Examples of functional endpoints suitable for incorporation into repeat dose toxicology studies

Organ system/function	Technique/method	Species
Cardiovascular system		
ECG interval durations, amplitude and morphology	Conventional 'snapshot' recordings in restrained animals	Dog; monkey; minipig ^{75,79-84}
ECG interval durations, amplitude and morphology	Surface electrodes using noninvasive telemetry in freely moving animals	Dog; monkey; minipig ⁸⁵⁻⁸⁸
Left ventricular function	Echocardiography	Dog; rat; minipig ⁸⁹⁻⁹⁴
Arterial blood pressure	Tail-cuff (restrained)	Dog; rat ^{95,96}
Arterial blood pressure	Ambulatory tail-cuff (telemetry)	Dog ^{93,97}
Nervous system		
Global neurobehavioural assessment	Functional observational battery or Irwin test	Rat; mouse; dog; monkey ⁹⁸⁻¹⁰⁸
Ambulatory activity (home cage)	RFID microchip transponder	Rat; mouse ¹⁰⁹
Ambulatory activity (novel arena)	Locomotor activity (photo cell beam breaks or videotracking)	Rat; mouse ^{100,104,108,110}
Motor coordination	Accelerating rotarod; beam walking; gait analysis	Rat ^{55,104,111}
Cognitive function	Avoidance paradigms (brief footshock stimulus on a single occasion)	Rat; mouse ^{104,112,113}
Auditory function	Brainstem auditory evoked response	Dog ¹¹⁴
Auditory function	Pre-pulse modulation of startle reflex; startle stimulus-response curves	Rat; mouse ^{54,104,115-118}
Visual acuity	Optomotor reflex	Rat; mouse ^{54,119}
Iris control	Pupil diameter; pupillary reflex response to light stimulus	Rat; dog ¹²⁰
Nociception	Tail flick latency	Rat; mouse ^{100,104}
Neuromuscular	Grip strength	Rat ¹⁰⁰
Salivation	Absorption into pre-weighed gauze	Dog ¹²¹
Respiratory system		
Respiration rate, inspiratory and expiratory times, tidal volume, minute volume, peak inspiratory and expiratory flows	Whole-body plethysmography	Rat; mouse ¹²²
(Ditto)	Inductive plethysmography	Dog; monkey ^{87,97,123,124}
Renal system		
Water intake, urine volume, urinary excretion of key electrolytes (Na ⁺ , K ⁺ , Cl ⁻). Estimated GFR and fractional excretion of electrolytes	Urine collection in metabolic cages	Rat ^{29,125}
Gastrointestinal system		
General assessment	Faeces weight, consistency, appearance	Rat; Dog ¹²⁶
Gastric emptying time; intestinal transit time; intestinal pressures	Telemetry capsule (e.g., SmartPill™; Bravo™)	Dog ^{127,128}
Hepatic system		
Bile acid analysis	Recoverable, swallowed thread	Dog ¹²⁹
General metabolic functions		
Rectal temperature	Rectal temperature probe (thermocouple or thermistor)	Rat; mouse; dog ¹³⁰
Interscapular temperature	RFID microchip transponder	Rat; mouse ¹³¹⁻¹³³
Glycaemic control	Glucose tolerance test (serial blood microsampling)	Rat; mouse; dog; monkey; minipig ¹³⁴⁻¹³⁹
Mitochondrial function	Blood glucose and lactate	Rat; mouse; dog; monkey; minipig ¹⁴⁰⁻¹⁴³
Oxygen consumption	Whole-body indirect calorimetry	Rat; mouse ¹⁴⁴

Techniques are either non- or minimally invasive with minimal impact on the animal and the study

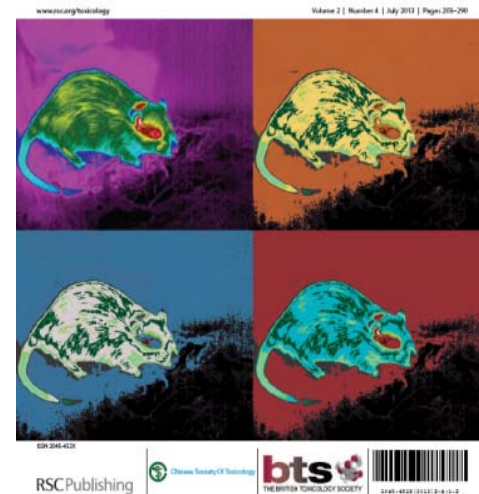
Third set of conclusions:

□ **Functional assessments** in repeat dose toxicity studies are entirely possible providing they are relatively unobtrusive

Functional assessments in repeat-dose toxicity studies:
the art of the possible *Toxicol. Res.*, 2013, **2**, 209

Will S. Redfern,* Lorna C. Ewart, Pierre Lainée,† Mark Pinches, Sally Robinson and Jean-Pierre Valentin

Toxicology Research



What we will cover today

- ❑ **Context – An overview of regulatory toxicity testing** to support first time in man (FTIM) dosing of small molecules
- ❑ **Can we reduce time/cost & still ensure human safety?**
 - ❑ FTIM study target organ profiles
 - ❑ Do we need the second species?
 - ❑ Do we need recovery?
- ❑ **Strategies & recent innovations**
 - ❑ Inclusion of safety pharmacology endpoints in general tox studies
 - ➡ ❑ Reducing attrition in the GLP phase of tox testing

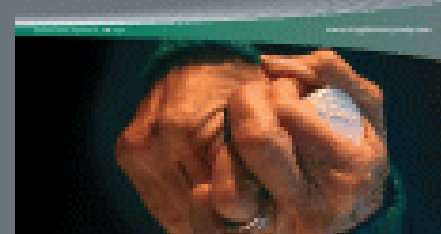


DRUG DISCOVERY
TODAY

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- Tailoring clinical path treatments for the elderly
- Tailoring FTIR sensors for clinical applications
- Progress-based error estimation in developmental modeling
- Human progress in research

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

Drug Discovery Today 19 March 2014 341-347

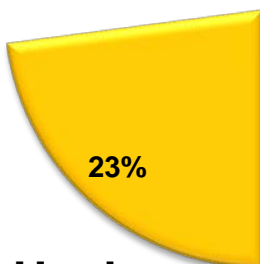
- ❑ Entry into the critical pre-clinical GLP stage of toxicology testing (FTIM studies) triggers significant R&D investment
- ❑ >20% of AstraZeneca's potential new medicines have stopped for safety reasons in this GLP phase alone
- ❑ How could we avoid at least some of these costly failures?

❑ An analysis of historical ‘stopping toxicities’ showed that **> 50%** were attributable to target organ toxicities emerging within two weeks of repeat dosing or to acute cardiovascular risks.

Not applicable

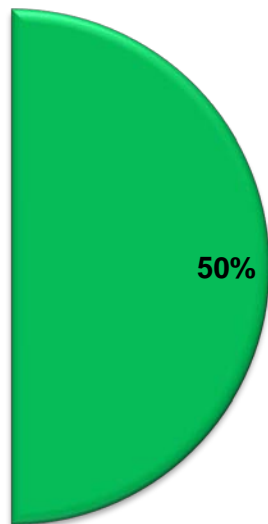


No



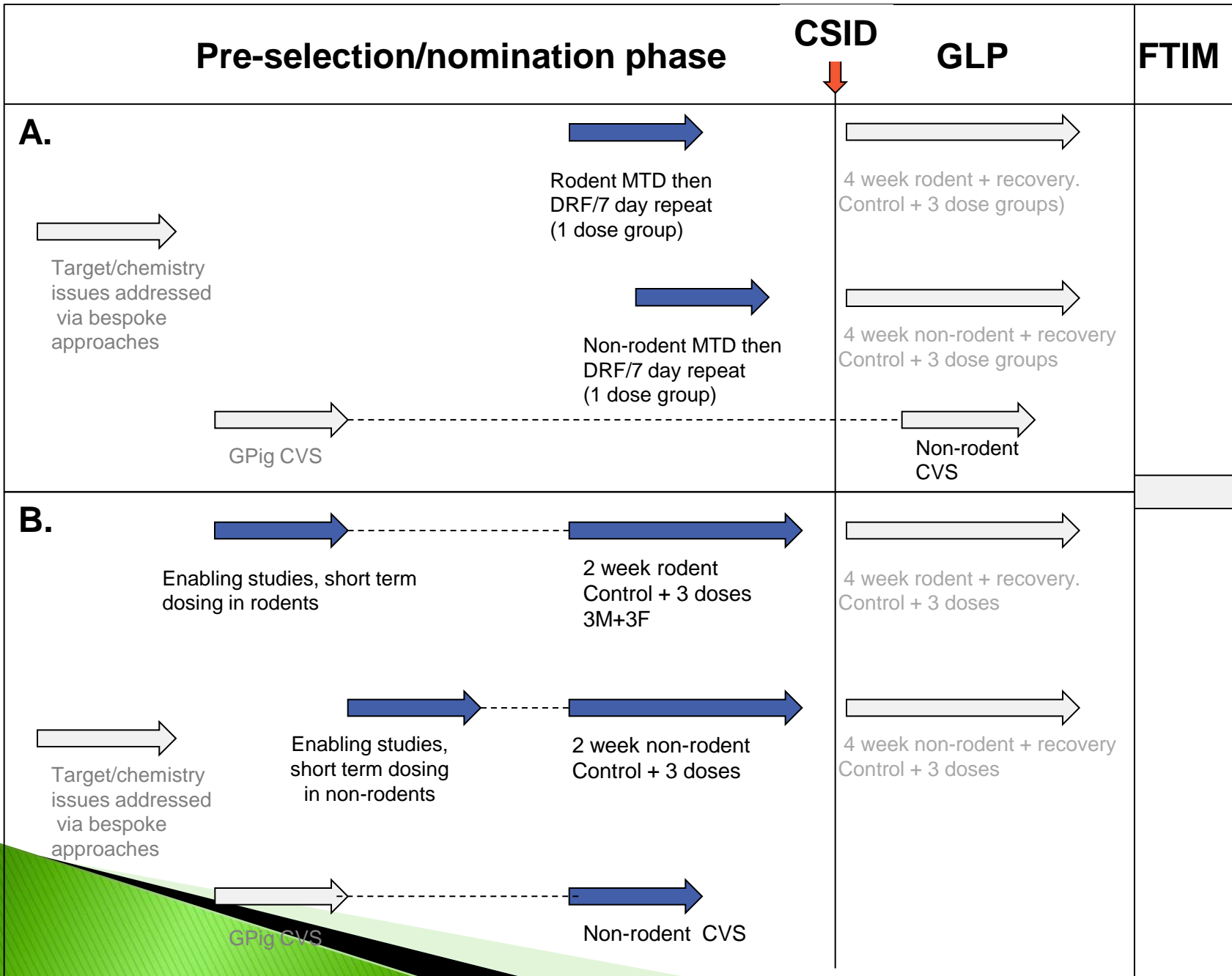
Unclear

Yes



Prediction	Number of CDs	Toxicity	Reason	
Yes	2	Hepatic	Detected in DRF study (less than 2 weeks)	
	1	GI	Detected in DRF study (less than 2 weeks)	
	1	CNS		
	1	Renal		
	4	CV pathology		
	2	Lung	Detected in DRF study (less than 2 weeks)	
	2	Muscle	Detected in DRF study (less than 2 weeks)	
	3	Unexplained deaths	Occurred in single dose and DRF studies	
	1	Pancreas	Detected in DRF study (less than 2 weeks)	
	1	Thyroid	Detected in DRF study (less than 2 weeks)	
	1	Lenticular	Detected in DRF study (less than 2 weeks)	
	1	Multiple target organ toxicities	Detected in DRF study (less than 2 weeks)	
	4	CV function	Detected in dog Telemetry	
	24 (50%)*			
	No – not detected at 2 weeks	1	CV Pathology	Not manifest until >3 weeks of dosing
		1	CNS	Not manifest until >3 weeks of dosing
1		Lung	Not detected after 2 weeks of dosing	
1		Reprotoxicity	Not detected after 2 weeks of dosing	
4 (8%)				
No – stopped for reasons other than toxicity	3	NA	Stopped for clinical safety	
	2	NA	Reactive metabolite detected	
	4	NA	Genetic Toxicology	
	9 (19%)			
Unclear	3	Renal	Uncertain if would be detected by 2 weeks	
	1	Liver	Uncertain if would be detected by 2 weeks	
	2	Lung	Uncertain if would be detected by 2 weeks	
	1	Muscle	Uncertain if would be detected by 2 weeks	
	1	Testicular	Uncertain if would be detected by 2 weeks	
	1	Adrenal	Uncertain if would be detected by 2 weeks	
	2	Multiple organ toxicities	Uncertain if would be detected by 2 weeks	
	11 (23%)			
TOTAL	48 (100%)			

❑ Redesign the nomination phase to reveal these issues earlier....

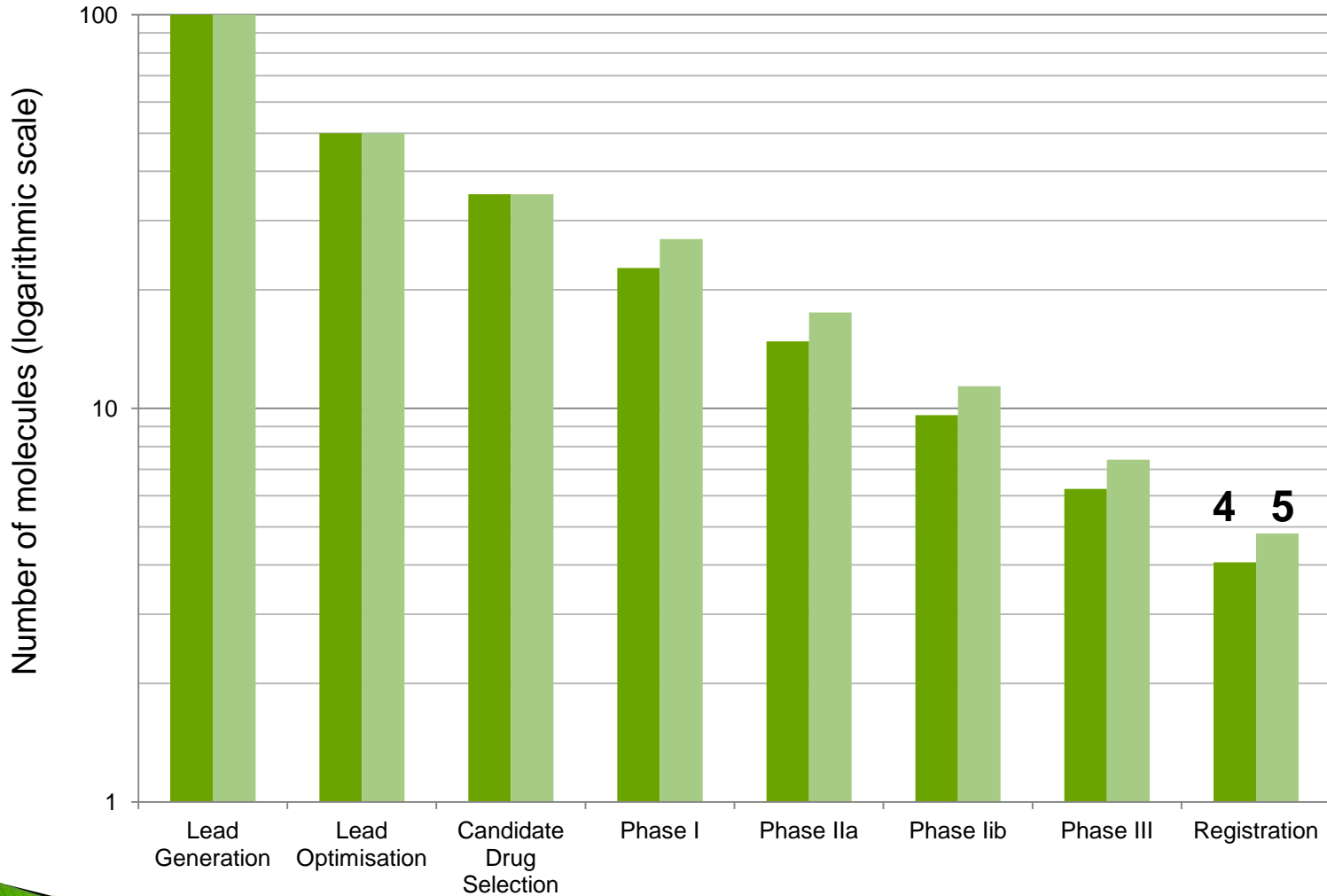


Modelling the impact on drug registration success rates of reducing attrition in the GLP Phase


	Numbers in	Probability of Success (POS)		Numbers in	Probability of Success (POS)
Lead Generation	100	50	➔	100	50
Lead Optimization	50	70		50	70
Candidate Selection	35	65		35	77
Phase I	23	65		27	65
Phase IIa	15	65		18	65
Phase IIb	10	65		11	65
Phase III	6	65		7	65
Registration	4	65		5	65

Table 2. Success in this candidate selection phase can be improved from 65% to 77% probability of success (POS) by a reduction of attrition due to toxicity from 24% to 12% (ie improve from 65 to 77% POS). Modelling is based on 100 drug projects entering lead generation then transitioning through 7 key stages each with its own probability of success (POS).

Modelling the impact on drug registration success rates of reducing attrition in the GLP Phase



Final conclusions:

- ❑ **Non-rodents** provide key data to support human safety assessment
 - ❑ **Move away from inclusion of recovery on the FTIM studies as default** - Scientific rationale, with enhanced knowledge of the CDs from the extended DRFs
 - ❑ **Functional assessments** in repeat dose toxicity studies are entirely possible providing they are relatively unobtrusive
 - ❑ Smart loading of **enhanced DRFs + non-rodent telemetry** reduces attrition in the GLP phase with overall benefits for the portfolio
- 

This CCT is about Science Based Decision Making to enhance regulatory success



**Take
home messages*

1. Guidelines are just that.....guidelines.....**avoid** 'box ticking tox'.....
2. **Do** employ innovative, science-based approaches to achieve FTIM quickly and efficiently while ensuring patient/volunteer safety
3. And **do** think beyond FTIM – ensure your non-clinical strategy is well set up for future clinical success in PhII and beyond....

Acknowledgements:

Outcome analyses (second species and recovery)

Steve Horner, Sally Robinson, David Lees, Katie Stamp, David Ryan, Richard Callander

Reducing Attrition

Stefan Kavanagh, Howard Mellor, Chris Pollard, Sally Robinson, Stefan Platz

Functional Assessments

Will Redfern, Lorna Ewart, Sally Robinson, Pierre Lainee, Mark Pinches, Jean-Pierre Valentin



What constitutes scientific justification for inclusion of recovery assessment in pre-clinical studies supporting first time in man (FTIM)?

Regulatory Toxicology and Pharmacology 70 (2014) 572-573.

Sally Robinson & Ruth Roberts

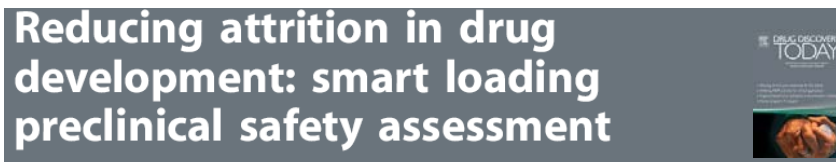
Recovery assessment in pre-clinical drug safety testing – a retrospective analysis of impact and timing

Regulatory Toxicology and Pharmacology 70 (2014) 270-285

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Target organ toxicities in studies conducted to support first time in man dosing: An analysis across species and therapy areas

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