



Safety Pharmacology Society

Welcome: Disease Models in Safety Pharmacology Webinar

We will begin at 11AM EST

- **Event will be recorded and available for viewing**
- **Call in to listen via phone**
 - select “info” folder tab to view call information, (must enter Attendee ID).
 - Participant audio lines are muted
- **40 minute presentation; reserving 20 minutes for Q&A**
 - Send your questions through the “Q&A” function, (expand to view).
 - Phone lines will be un-muted at the end of the presentation.
 - Questions will be answered at the end the presentation.

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Animal Models of Disease for Safety Testing – SPS Webinar

R.M. Wallis

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Presentation

- Objectives of Safety Pharmacology Studies
- Understanding translation and decision making
- Animal models of disease
- Confidence in translation
- Conclusion

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Objectives of Safety Pharmacology Studies

- **1.5 Definition of Safety Pharmacology**
- ICH S7A – ‘Safety pharmacology studies are defined as those studies that investigate the potential undesirable pharmacodynamic effects of a substance on physiological functions in relation to exposure in the therapeutic range and above’
- **2.1 Objectives of Studies**
- The objectives of safety pharmacology studies are: 1) to identify undesirable pharmacodynamic properties of a substance that may have relevance to its human safety; 2) to evaluate adverse pharmacodynamic and/or pathophysiological effects of a substance observed in toxicology and/or clinical studies; and 3) to investigate the mechanism of the adverse pharmacodynamic effects observed and/or suspected. The investigational plan to meet these objectives should be clearly identified and delineated.
- Defining and understanding the pharmacology of test substance
 - Minimise variables such that we study the effect of the compound
 - Consistent testing paradigm such that we can compare across compounds

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Objectives of Safety Pharmacology Studies

- Prevention of serious ADR in FIH studies
- Understanding the concentration-response relationship for any effects on major physiological systems that may be predictive of AEs in man
- In combination with other safety data, safety pharmacology should be used to select the starting dose for FIH
- Support mechanistic understanding of AEs in clinical trials
- Understanding safety risk in high risk patient populations on long term therapy



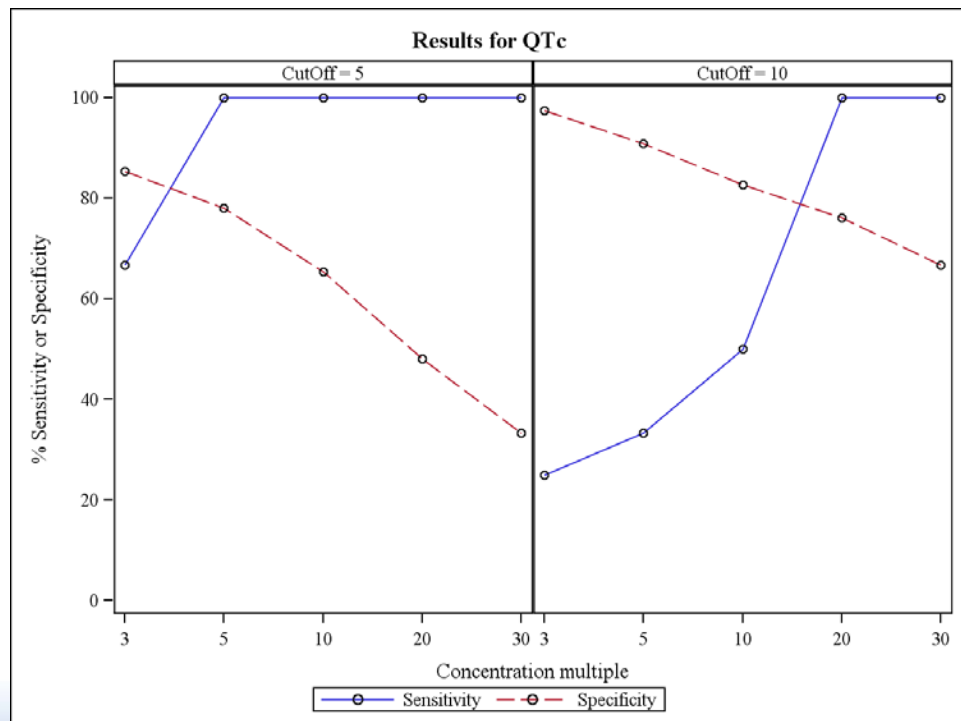
Understanding translation from animals to humans

- Defining drug effects in humans is the goal
 - Use of animals is an essential stepping stone to select the best drug targets and compounds
 - Animals and non-clinical data are used for decision making in the above
- Effective decisions can only be made when we understand the translation from animals to humans
 - SPS has existed for 10 years
 - Ongoing activities to define translation of core S7A studies
 - ECG/arrhythmias – HESI
 - BP/HR, CNS/Pulmonary - AMF



Understanding translation

	Model/Parameter within model		
Score	1	2	3
Matching the clinical end point x2	Cannot or do not measure same end point in animals and human	Measure same physiological end point, but not the same measure	Measure same end point in humans and animals
Matching the pathway/mechanism (conservation of pathways) x1	Target/pathway not validated or relevant in humans	Target/pathway present in model and hypothesised to be relevant in man	Target pathway known and relevant in model and man
Matching the physiology x1	Pathway present in model, but relevance to man is unknown	Pathway present and functional in model, but unknown direction and magnitude	Pathway present and functional in the same direction and magnitude





Translation of animal efficacy models

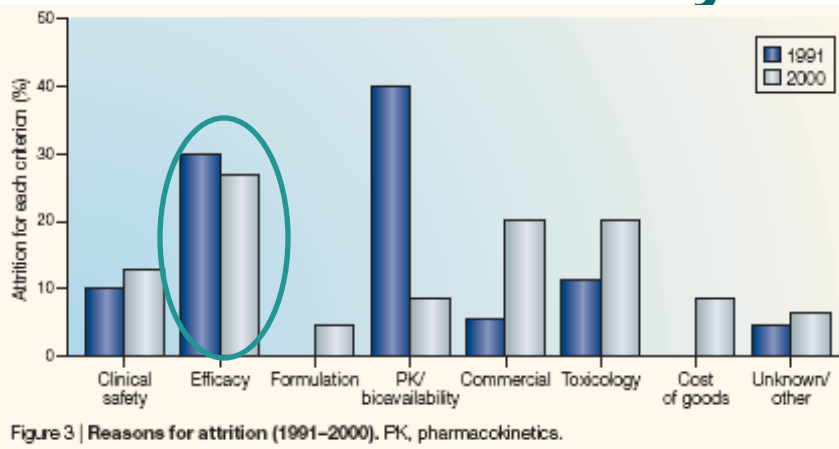


Figure 3 | Reasons for attrition (1991–2000). PK, pharmacokinetics.

Kola & Landis (2004) *Nature Reviews: Drug Discovery* 3: 711-715.

- Phase II efficacy remains a major cause for compound attrition
- Nearly all compounds are tested in 'animal models of disease' to raise CIR prior to human testing
 - If animal models of disease are predictive of human outcome then phase II survival would be higher
- What makes us think safety testing in animal models of disease would be better than efficacy?



How do we model human disease?

- Human disease is multi-factorial
 - Genetic
 - Environmental
 - Co-morbidity
 - Concomitant therapy
- Animal models of disease cannot reflect these variables e.g. diabetes



Animal models of CV disease

Diet induced obesity	Corpulent rats			Genetically modified mice	Other models
Primate	Fatty Zucker rat (fa/fa)			ApoE ^{-/-}	SHR
Dog – high fat diet	Zucker diabetic fatty (ZDF) rat			LDLR ^{-/-}	SHR & sucrose
Rabbit – high cholesterol diet	SHROB	SHR/N-cp	La/N-cp	SR-BI KO	Syrian hamster +/- fructose
Rat – high fat diet	SHHR/Mcc-cp			<i>db/db</i> mouse	Sand rat
Rat – fructose diet	JCR:LA-cp			<i>ob/ob</i> mouse	CETP transgenic rats
Swine – high sugar diet	SPSHR x Zucker fatty rat				

Thanks to Nick Edmunds



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How could we use 'perturbed animals'

- Having defined the pharmacology of a compound in normal animals, we often ask the question what would the consequence be in
- Excessive prolongation of QT interval is associated with TdeP
 - Chronic AV-blocked dog
 - Methoxamine rabbit
 - Are these animal models of disease?
- Human TdeP is associated with known risk factors
 - Genetics
 - Ion changes – K and Mg
 - Gender
- Models effect of excessive QT prolongation
 - Human data to suggest QT prolongation >500msec significantly increases risk of TdeP
 - In normal dogs dofetilide will induce a maximum QT prolongation to ~350msec
 - In the AV-blocked dog dofetilide will increase QTc >500msec and induce TdeP

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Where do you stop with 'animal models of disease'?

- Diabetes
 - Test all compounds that may be co-prescribed in diabetes?
 - Probably test CV active compounds – but what value does this add once we have defined a compound has a CV risk
- Asthma
 - Why would we test compound safety in animal models of asthma?
 - Concern would be raised if altered lung function was observed in normal animals
 - What value would this add?
- Alzheimer's
 - Are there good models of disease?
 - Why would we be concerned? If we observed cognitive effects in normal animals.



Conclusions

- SP is about defining the pharmacology of NCEs and understanding this risk to humans
- Understanding translation to humans is key to make decisions on compound progression
- Human disease is complex and cannot be truly modeled in animals
- Understanding translation to humans of safety findings in animal models of disease is almost impossible
 - Too many variables
 - Insufficient compounds