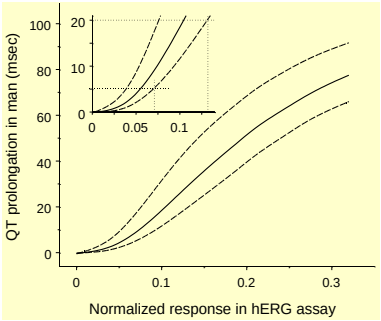
The role of non-clinical assays in determining the level of clinical QT assessment

Rob Wallis, Executive Director, Drug Safety Research and Development, Pfizer

(robwallis120@hotmail.com)

Introduction

- Role of non-clinical studies are to identify signals of risk for humans
  - Magnitude of signal that is a concern
  - FIH vs. TQT study
- Inhibition of hERG channel is a significant risk for QT prolongation, especially with evidence of translation e.g. Purkinje fiber or *in vivo* data



	Man	Dog	G.Pig
E_{max} (ms)	105	59	41
E0 (ms)	386	212	148
% increase	27	28	28

10 msec in human = 5-6 msec in dog?

- Non-hERG mediated QT prolongation is less reliably detected in non-clinical assays e.g PDE5i. However, these may be detected in FIH studies
- A number of datasets are becoming available to study translation of non-clinical data to the clinic

Understanding translation

	Animal +ve	Animal -ve	
Human -ve	False +ve (FP)	True -ve (TN)	Assay specificity TN/(TN+FP)
Human +ve	True +ve (TP)	False -ve (FN)	Assay sensitivity TP/(TP+FN)
	+ve predictive value TP/(TP+FP)	-ve predictive value TN/(TN+FN)	

Knowing the clinical outcome is +ve or –ve, what are the chances of the assay is +ve or –ve?

If the assay is +ve or –ve, what are the chances of the compound being +ve or –ve in humans?

Animal Model Framework

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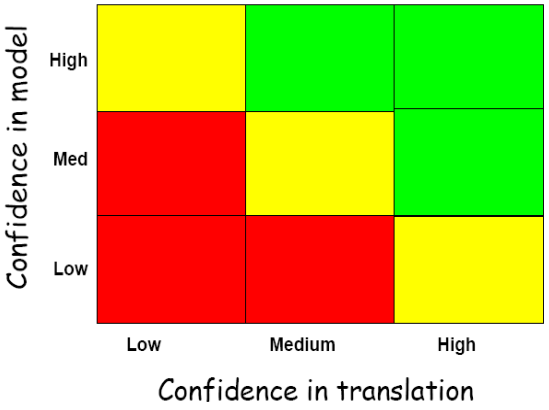
Original article

A framework to assess the translation of safety pharmacology data to humans

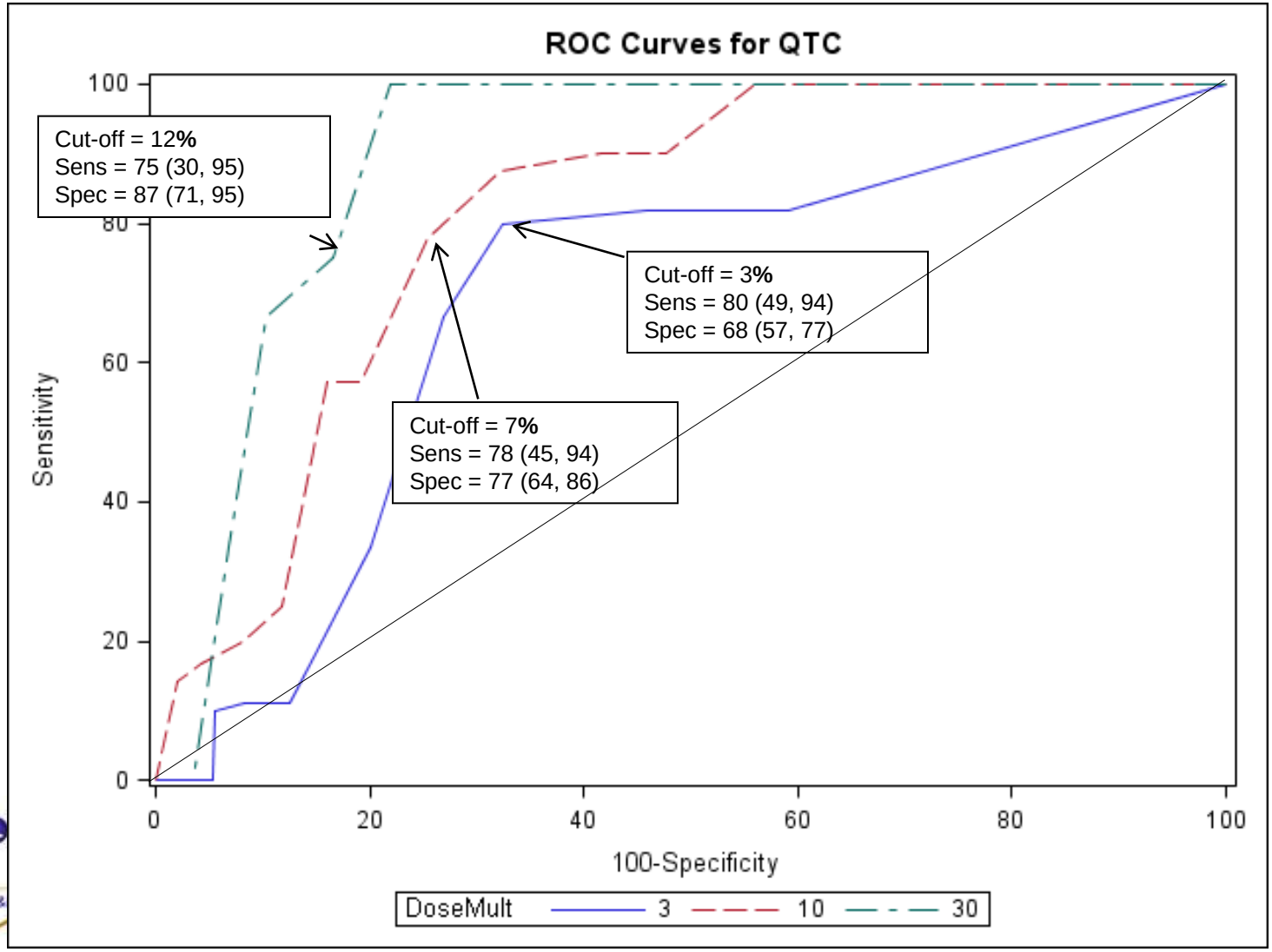
Jean-Pierre Valentin [a,1], Russell Bialecki [b], Lorna Ewart [a,*,1], Tim Hammond [a], Derek Leishmann [c], Silvana Lindgren [d], Vicente Martinez [e], Chris Pollard [a], Will Redfern [a], Rob Wallis [f]

[a] Safety Assessment UK, AstraZeneca R&D Alderley Park, Macclesfield, SK10 4TG, United Kingdom
[b] Safety Assessment US, AstraZeneca R&D Wilmington, DE 19850, USA
[c] Eli Lilly & Co., P.O. Box 708-2001 West Main Street, Greenfield, IN 46140-0708, USA
[d] Safety Assessment Sweden, AstraZeneca R&D Södertälje, S-151 85 Södertälje, Sweden
[e] Department of Cell Biology, Physiology and Immunology, Unit of Physiology, Veterinary School and School of Biosciences, Universidad Autonoma de Barcelona, 08193 - Bellaterra, Barcelona, Spain
[f] Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent, UK

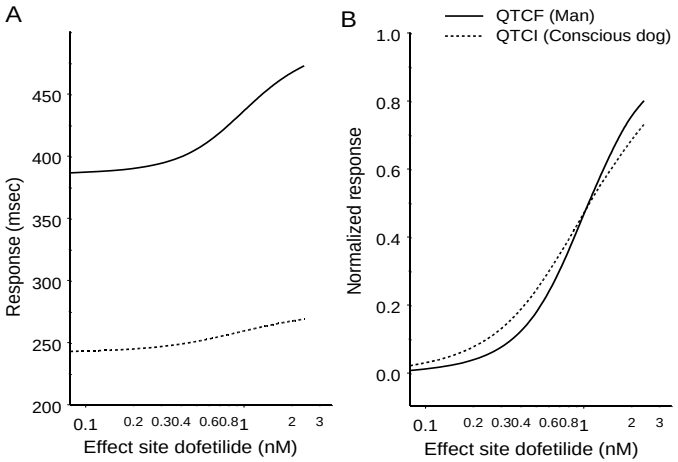


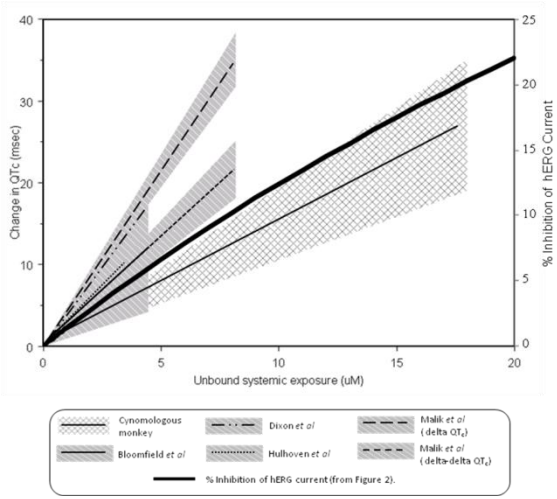
- Cross-pharma dataset of 114 compounds
- FIH data - +ve or –ve for QTc changes
  - 14 compounds reported an increase QTc and 2 compounds decrease
  - No quantification of the magnitude
- Reviewed dog telemetry data
  - Magnitude of change at multiples of human exposure

The dog telemetry model adequately predicts QT changes in man based on the data from the 114 compounds.



TI-Pharma – PK/PD Approach





- Developing PK/PD models for ~6 compounds across species (dog, monkey and man) and applying a probabilistic analysis for a QT effect
- Attractive approach
  - Exposure response
  - Time course
  - Other factors e.g. metabolites

hERG Translation to dog

Compound	hERG IC_{20} μM	Modelled [μM] for 10 msec change in dog	Fraction of hERG IC_{20}
A	6.9	2.3	0.33
B	0.57	0.29	0.51
C	2.04	0.63	0.31
D	1.6	0.4	0.23
E	16.7	7.6	0.45
F	2.5	2.2	0.9
Moxi	12.8	3.5	0.27

Predicting QTc Changes in Human TQT study

- 26 compounds tested in Pfizer 'TQT studies'
  - Including 7 comparator agents/positive controls
- All studies were designed to rule out a 7 to 10 msec change in QTc
- Positive QTc study was defined if the QTc change exceeded the pre-defined sensitivity
- Data derived from clinical study report
- Non-clinical analysis based on
  - 1/10 hERG IC_{50} value
  - Purkinje fibre Studies powered to detect 8% change with 90% power using n=5
  - *In vivo* studies powered to detect ~5 msec QTc change with 90% power using n=4 cross over design

Predicting QTc Changes in Human TQT study

Multiple of clinical [ ]	hERG		Purkinje		Dog	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
X2	0.86	0.92	0.25	1.0	0.63	0.9
x10	0.92	0.5	0.44	0.82	0.83	0.29
X30	0.9	0.17	0.40	0.60	-	-

Issues

- No harmonized study design
  - For some compounds inhibition of hERG current is very much protocol dependent – potency can vary by ~10-fold
    - Not an issue if taken as safety signal, critical for understanding potential exposures that may prolong QTc interval
- Most *in vivo* CV studies are designed to detect large effects of concern for FIH studies. May not have appropriate assay sensitivity to detect changes of 5 to 10 msec
  - Potential to detect larger effects at higher multiples of human exposure
    - May not study such high multiples
    - Potential to dismiss effect as not relevant because only observed at high doses
    - Assumes some understanding of exposure response relationship
- Issue of assay sensitivity has been discussed at Safety Pharmacology Society sponsored workshop
  - Key recommendations
    - Define hypothesis to be tested
      - E.g. detect a 5 msec change in QTc or 10% (25 msec)
    - Does the study design have the potential to detect desired effect?
      - Power calculations
    - Understand ability of the study design to detect known agents of concern
      - Reference agent
    - Support conclusions based on ability of the specific study to detect change

Conclusions

- Non-clinical assays can detect agents that prolong QT interval via hERG inhibition
  - Robust in vitro assays
  - Assays to confirm translation (re-verapamil)
- More robust application of PK/PD modeling can define exposure response relationships to aid translation to man
  - Model potential exposures to cause ‘small changes’ of concern in the TQT study
- Need to prospectively define study objectives
  - Cannot claim lack of QT signal of regulatory concern if the *in vivo* assay is not appropriately powered
- Non-clinical assays do not detect all QTc prolonging agents e.g. mild vasodilators – PDE5i
  - These mechanisms are detected in FIH studies
- Combination of robust non-clinical and FIH studies has the potential to detect small QT changes of regulatory concern.