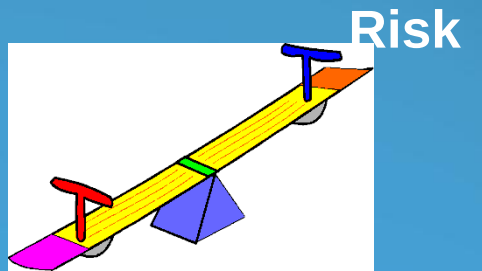
EMA EFPIA workshop
Break out Session no. 2

Topic 2: The integration of data (e.g. across studies or clinical and in-vitro data) using M&S along with reasonable assumptions can provide evidence for evaluation of efficacy/safety risks without the need for a separate study.

Integration of data using M&S

Use of M&S with existing information (data, physiological /mechanistic knowledge) and reasonable assumptions will allow for improvements and efficiency in informed decision making to improve the outcomes for patient safety and efficacy.

How do we provide a risk versus benefit approach based on M&S that demonstrates a probabilistic assurance of minimizing risk while maximizing benefit, knowing that risk will not be zero.



Integration of data using M&S

- How can M&S, including integration of preclinical and early clinical data, improve our approach to QT assessment?
- What data is needed (in-vitro/ human/ physiologic), that when combined with a M&S approach and reasonable assumptions, would improve our approach to assessment of clinical pharmacology (special populations, DDI, etc.)?

Can M&S improve our approach to QT assessment?

Background

- In the late 1990s the arrhythmia torsade des pointes (TdP) and QTc prolongation emerged as a drug safety issue
- No regulatory guidelines existed until a CHMP Points to Consider Document in 1997 – needed to measure QTc
- ICH S7A in 2000 left out QTc measurement since this topic was still evolving
- ICH S7B and E14 implemented together in 2005 – ironically no link between these in that all compounds require TQT study (E14) regardless of nonclinical findings (S7B)
  - Can this change?
  - ICH E14 adopted in Japan 2010
- **Can an integrated approach using M&S be helpful in understanding the risk of QT prolongation?**

Can M&S improve our approach to QT assessment?

Issues

Currently – Only a Thorough QT study or positive early clinical study at therapeutic doses is acceptable as characterization of the risk of QT prolongation.

- Preclinical data does a good job at predicting risk of QT prolongation… but not good enough (false negative =15%?).
- Early clinical data does a good job at predicting risk of QT prolongation… but not good enough (false negative <10%?).
- Can a 'totality of evidence' approach, integrating preclinical and early clinical data using M&S, appropriately characterize the QT interval?

Bayes' theorem applied to drug development and QT data

What is the positive and negative predictive value of Phase 1 QT data, given that preclinical data does a fairly good (but not 100%) job of predicting risk?

For sake of argument, say there is a good margin to clinical concentrations (10x?):

Sensitivity of preclinical package hERG + dog = .90 (False negative rate = 10%)

Specificity of preclinical package hERG + dog = .60 (False positive rate = 40%) ****These compounds are usually KILLED**

**Specificity decreases (FP increase) with increased cutoff for assay (*i.e.*↑from 10 to 30 fold margins)

Bayes' theorem applied to drug development and QT data

What is the positive and negative predictive value of Phase 1 QT data, given that preclinical data does a fairly good (but not 100%) job of predicting risk?

For sake of argument, say there is a margin to clinical concentrations (2x):

Sensitivity of Phase 1 PK/PD= .95 (False negative rate = 5%)

Specificity of Phase 1 PK/PD = .90 (False positive rate = 10%)

We test a Preclinical NEGATIVE compound in Phase 1…

Bayes' theorem applied to drug development and QT data

Given negative preclinical, prevalence (prior probability) is 10%

		Actual QT Effect present: Present	Absent	total
Phase 1 Results	Positive	9.5	9	18.5
	Negative	.5	81	81.5
	total	10	90	100

Positive Predictive Value = TP/ (TP + FP)

9.5/(9 + 9.5) = .51 51%

Negative Predictive Value = TN/ (FN + TN)

81/81.5= .994 99.4%

Bayes' theorem applied to drug development and QT data

What is the positive and negative predictive value of TQT data, given that preclinical and Phase 1 data does a fairly good (but not 100%) job of predicting risk?

For sake of argument, say there is good power to exclude a positive conc/QT relationship:

- Sensitivity of TQT study = .95 (false negative rate= .05)
- Specificity of TQT study = .90 (false positive = 10%)

We test a Preclinical and Phase 1 NEGATIVE compound in Phase 1…

Bayes' theorem applied to drug development and QT data

Given negative preclinical and phase 1 clinical, prevalence (prior probability) is .6%

		Actual QT Effect present		
		Present	Absent	total
TQT Results	Positive	.57	9.94	10.51
	Negative	.03	89.46	89.49
	total	.6	99.4	100

Positive Predictive Value = TP/ (TP + FP)

.57/(9.94 + .57) = .054 5.4%

Negative Predictive Value = TN/ (FN + TN)

89.46/89.49= .999 99.9%

Bayes' theorem applied to dru development and QT data

Given negative preclinical and phase 1 clinical, prevalence (prior probability) is .5%

Positive Predictive Value = TP/ (TP + FP)

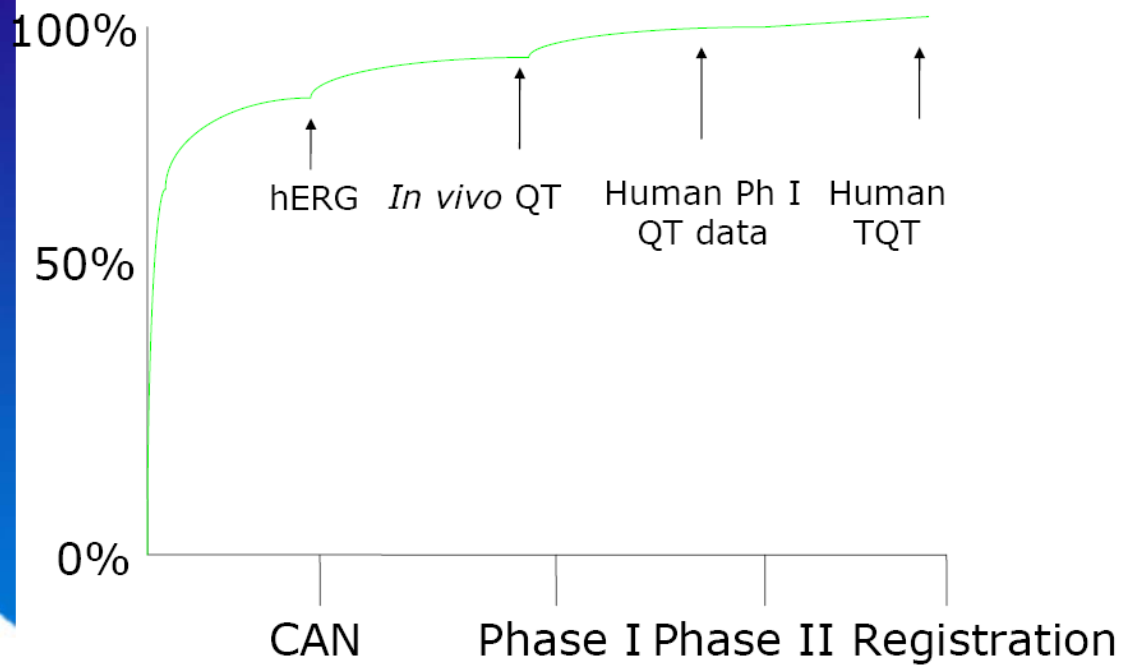
.475/(9.95 + .475) = .045 4.5%

Negative Predictive Value = TN/ (FN + TN)

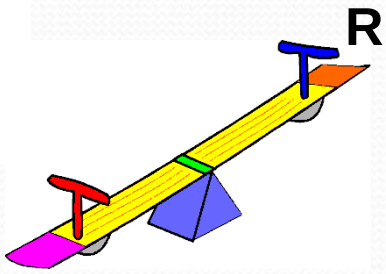
89.55/89.8= .997 99.7%

The addition of the TQT study increased the negative predictive value from 99.5% to 99.7%.

Resolving Uncertainty in Predicting QTc



- 80% of the uncertainty about QTc outcome resolved by hERG assay
- 95% following the in vivo study
- 100% following FHD



Slide courtesy of Derek Leishman, Ph.D.
Eli Lilly and Co

Integration of data using M&S

- Totality of evidence adds to the negative and positive predictive values of the characterization of QT
- Other issues:
  - Concentration response modeling of Phase 1 data
    - Is a negative relationship to be believed without a positive control?
    - Is a positive relationship to be believed if it supplies a significant margin of safety (and can serve as a negative study)?
  - Lack of 'validation' of Phase 1 data
    - Inconsistent preclinical or clinical data aquistition/analysis
    - Empiric approach - Collect data set demonstrating ability of Phase 1 to predict TQT
    - Incentive approach – Write guidance that allows sponsors to delay TQT until Phase 3, or emit TQT altogether, if appropriate preclinical or clinical data are acquired.

Integration of data using M&S

- How can M&S, including integration of preclinical and early clinical data, improve our approach to QT assessment?
- What data is needed (in-vitro/ human/ physiologic), that when combined with a M&S approach and reasonable assumptions, would improve our approach to assessment of clinical pharmacology (special populations, DDI, etc.)?

Can M&S be used in clinical pharmacology to improve understanding of patient subpopulations?

- Analysis and design of modeling exercise should be fit for purpose
  - Rigid, box checking, studies can be an inefficient method of adding information to existing risk:benefit relationship.
- Risk versus benefit approach based on M&S can demonstrate a probabilistic assurance of minimizing risk while maximizing benefit, knowing that risk will not be zero.
  - Careful analysis of probability of impacting clinical risk needs to be performed.

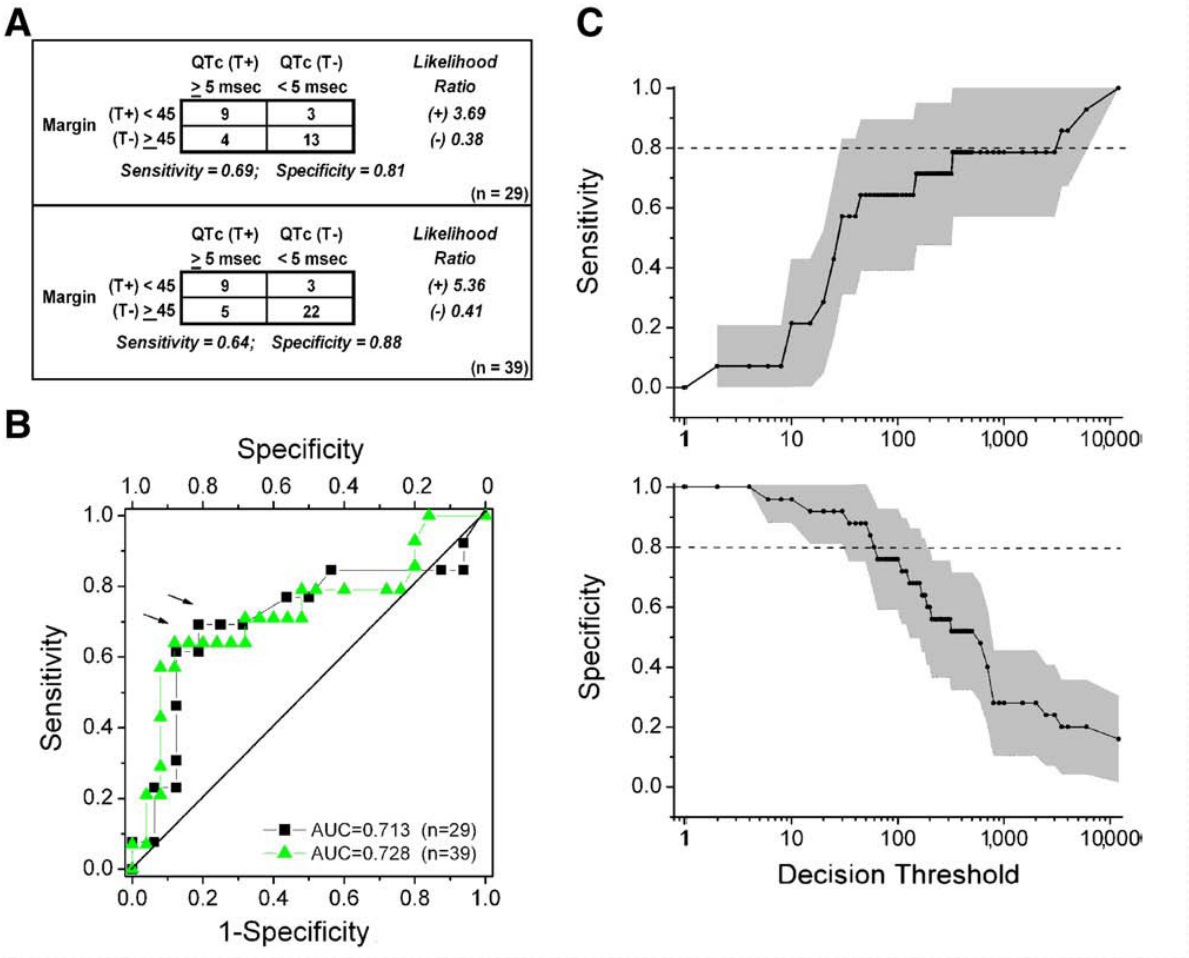
Questions:

- What can M&S do to improve our approach to QT prolongation risk?
  - Are we ready to trust a combined, 'totality of evidence,' approach to QT assessment?
  - Are we ready to trust concentration response models to predict negative and positive early phase data?
- Can M&S be used in clinical pharmacology to improve understanding of patient subpopulations?
  - Are we ready to trust models to suggest dosing recommendations for a patient population (interpolation)?
  - Are we ready to trust models that predict interactions in an untested population (extrapolation)?

Back up Slides

- Acknowledgement: Thanks to Derek Leishman, Ph.D. Eli Lilly and Company for many of the slides in the back up deck.

Predicting TQT = hERG Margin



Optimal at 45-50 fold margin between hERG IC_{50} and unbound plasma concentration

Gintant, G. (2011) An evaluation of hERG current assay performance: Translating preclinical safety studies to clinical QT prolongation. Pharmacology & Therapeutics 129,109–119

Predicting TQT – Using IC_{10} Value

Pre-clinical data translation to man

- hERG
  - Wallis (2010)
  - Analysis of 19 compounds (11 with +ve TQTS; 8 with –ve TQTS)
  - Did hERG IC_{10} predict TQTS outcome within 2-fold C_{max} free?

		Human			
		Neg	Pos		
Pre-clin	Neg	6	2	Predictive capacity	0.79
	Pos	2	9		
		Specificity	Sensitivity		
If a compound is 'negative' in human, what is the probability that the animal model will correctly identify it.		0.75	0.82	If a compound is 'positive' in human, what is the probability that the animal model will correctly identify it.	

The IC_{10} value is approximately 1/9th of the hERG IC_{50}

Slide from Chris Pollard (AZ) based on Wallis, R. (2010) Integrated risk assessment and predictive value to humans of non-clinical repolarization assays. British Journal of Pharmacology, 159, 115–121

In Vivo QTc Translation to Man

C Pollard Presentation May 2010

Pre-clinical data translation to man

- *In vivo* models – conscious telemetered dog
  - Hanson et al. (2006) - ILSI-HESI
  - Analysis of 12 compounds (6 with TdP risk; 6 without)
  - Did effect on QTcF predict TdP risk?
  - Significant prolongation = TdP risk; NS prolongation = no TdP risk

		Human			
		Neg	Pos		
Pre-clin	Neg	6	0	Predictive capacity	1.00
	Pos	0	6		
		Specificity	Sensitivity		
		1.00	1.00		

If a compound is 'negative' in human, what is the probability that the animal model will correctly identify it.

If a compound is 'positive' in human, what is the probability that the animal model will correctly identify it.

- Based on a cross pharma initiative through ILSI/HESI
- In Vivo assay appears very predictive of which compounds might be associated with TdP
  - What about concentration where effects occur in animals and man?

In Vivo QTc Translation to Man

C Pollard Presentation May 2010

Pre-clinical data translation to man

- *In vivo* models – conscious telemetered dog
  - Toyoshima et al. (2005) - PRODACT
  - Analysis of 21 compounds (11 with TdP risk; 10 without)
  - Did effect on QTc predict TdP risk?
  - Significant prolongation = TdP risk; NS prolongation = no TdP risk

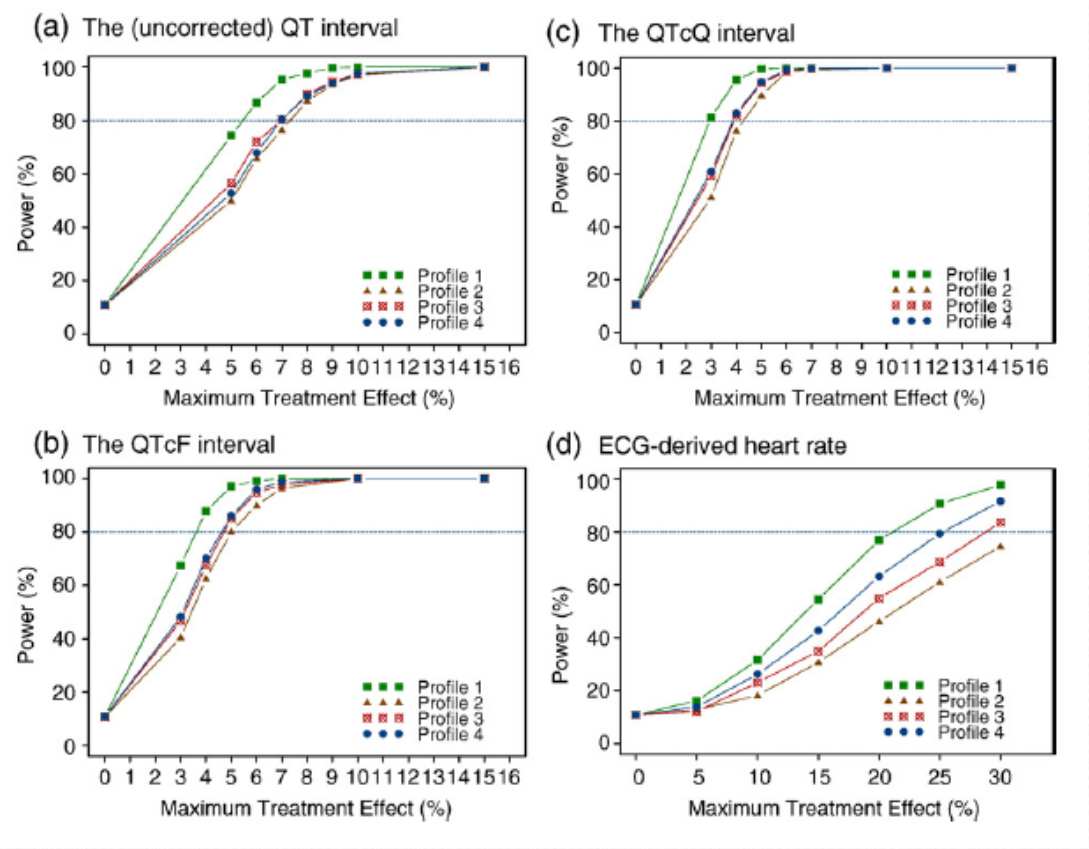
		Human			
		Neg	Pos		
Pre-clin	Neg	9	0	Predictive capacity	0.95
	Pos	1	11		
		Specificity	Sensitivity		
		0.90	1.00		

If a compound is 'negative' in human, what is the probability that the animal model will correctly identify it.

If a compound is 'positive' in human, what is the probability that the animal model will correctly identify it.

- Based on a cross pharma and CRO initiative in Japan called PRODACT
- Again trying to predict compounds associated with TdP
  - Likely requires a large QTc change in man? See Bednar et al 2002. These authors suggested most TdP associated with QTc of 500ms or greater
  - If one can only detect changes of reasonable magnitude in vivo the predictive value is still very high if attempting to predict dramatic effects in man

Statistical Power ILSI/HESI (c.f. Hanson et al 2006)



- n=8, 4 x 4 Latin Square, doubled
- 15 ECG complexes averaged at 7 time points
- 80% Power to detect 7% increment of QT, a 5% increment of QTcF, and a 4% increment of QTcQ
- Based on 8 animals and 4 treatments the data density is around 420 ECGs from around 400K possible complexes (0.1%)

Chiang, et al 2007 J Pharmacol Toxicol Methods, 56, 95-102

In Vivo QTc Translation to Man

C Pollard Presentation May 2010

Pre-clinical data translation to man

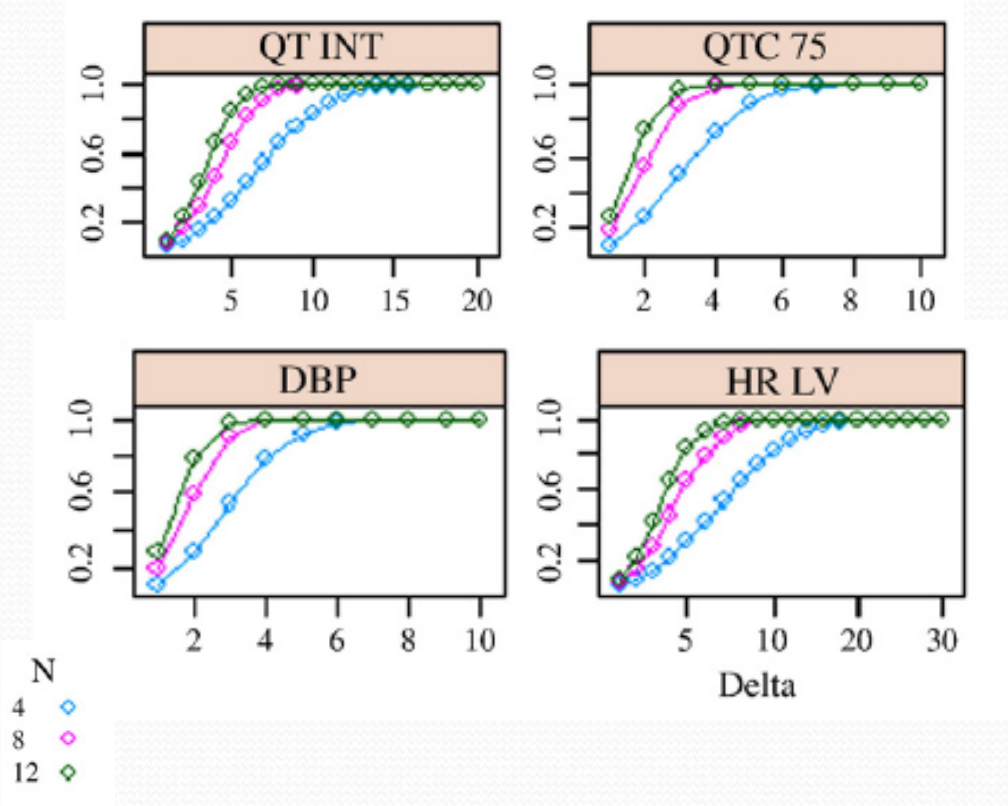
- *In vivo* models – conscious telemetered dog
  - Wallis (2010)
  - Analysis of 19 compounds (11 with +ve TQTS; 8 with –ve TQTS)
  - Did effect on QTc predict TQTS outcome within 2-fold C_{max} free
  - > 10 ms prolongation = +ve TQTS; < 10 ms prolongation = -ve TQTS

		Human			
		Neg	Pos		
Pre-clin	Neg	6	2	Predictive capacity	0.79
	Pos	2	9		
If a compound is 'negative' in human, what is the probability that the animal model will correctly identify it.		Specificity	Sensitivity	If a compound is 'positive' in human, what is the probability that the animal model will correctly identify it.	
		0.88	0.82		

*

- Recent publication based on 19 TQT (Thorough QT) type studies
- Attempting to predict a QTc change of between 5 and 10ms in man
  - Concentration and margin based since uses Cmax value from TQT study
  - Still good predictive capacity
  - Improved by using additional data in an integrated assessment as suggested in ICH S7B

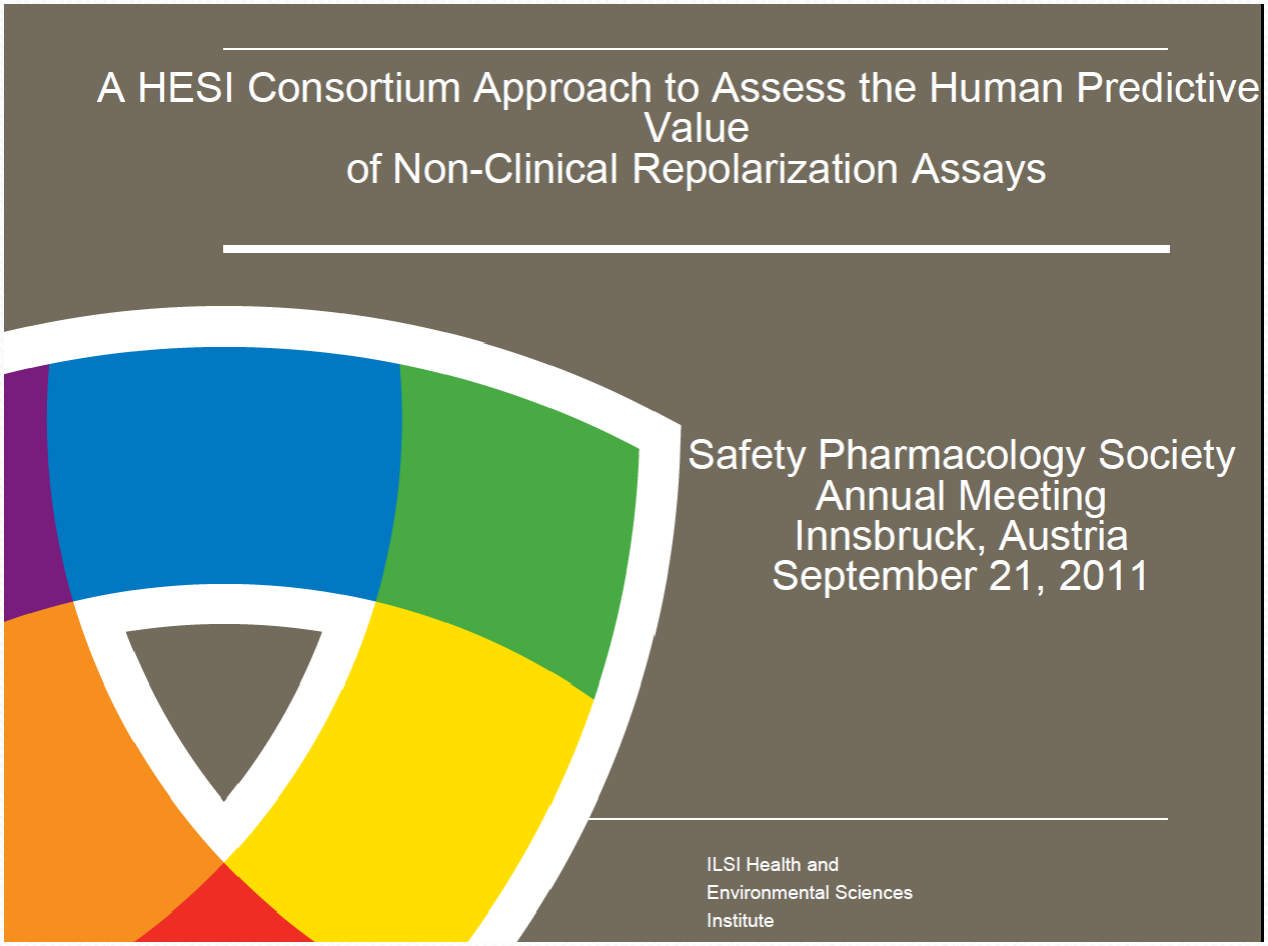
Statistical Power Pfizer (c.f. Wallis, 2010)



- n=4, 4 x 4 Latin Square
- All available ECG complexes, superinterval average
- 80% power to detect the following changes: HR (±10 bpm), LV+dP/dtmax (±375mmHg/s),MBP (±5 mmHg) and QTc (±4 ms; approx 2%)
- Based on 4 animals and 4 treatments the data density is likely around 300K ECGs from around 400K possible complexes (75%)

Sivarajah, et al 2010 J Pharmacol Toxicol Methods, 62, 12-19

ILSI/HESI 2011



- Presentation from John Koerner (FDA)
- Co-chair of this ILSI/HESI Group
- Strong partnership with FDA

Objectives

Project Objectives

1. To assess the concordance between non-clinical repolarization assays and clinical measures of QT interval prolongation

2. To investigate the mechanisms for any discrepancy identified between non-clinical and clinical results and to determine viable and successful alternative approaches to identify these compounds

3. To assess the proarrhythmic potential of such compounds

ILSI Health and
Environmental Sciences
Institute

- Ultimate goal to eliminate TQT for genuinely negative compounds
- Potentially limit attention to compounds thought to be proarrhythmic

Concordance Phase

Stage 1 Strategy

- **Generate datasets containing non-clinical and clinical QT information**
- **Public-private collaborative data collection**
- **4 approaches**
  1. **Data submitted to FDA (76 drugs)**
  2. **Additional data input from Pharma companies**
  3. **Use of data from previous initiative (Hanson et al) (12 drugs)**
  4. **Data available from the literature (17 drugs)**

ILSI Health and Environmental Sciences Institute

- Focus of the work to date
- All 3 & 4 approaches have largely completed
- Approach 1 in progress
- Approach 2 on hold – desire was for Phase 1 data

FDA Database Contents

FDA Database Contents

	TQT	hERG	APD	Non-Clinical ECG
# of Studies	76	73	41	73
Quality Assurance	22	68	41	30
Date Range	2005-2010	2000-2011	1994-2007	1993-2007
% Post-ICHS7B	100%	49%	10%	36%

Studies with all 4 endpoints: 28
Studies with hERG, ECG, & TQT: 57

Preliminary analysis is discussed in subsequent slides
- 22 drugs: 10 positive TQT, 12 negative TQT

ILSI Health and
Environmental Sciences
Institute

- FDA have supported this well but competing demands are an issue

Concordance to Date

Preliminary Concordance Summary (22 Drugs)

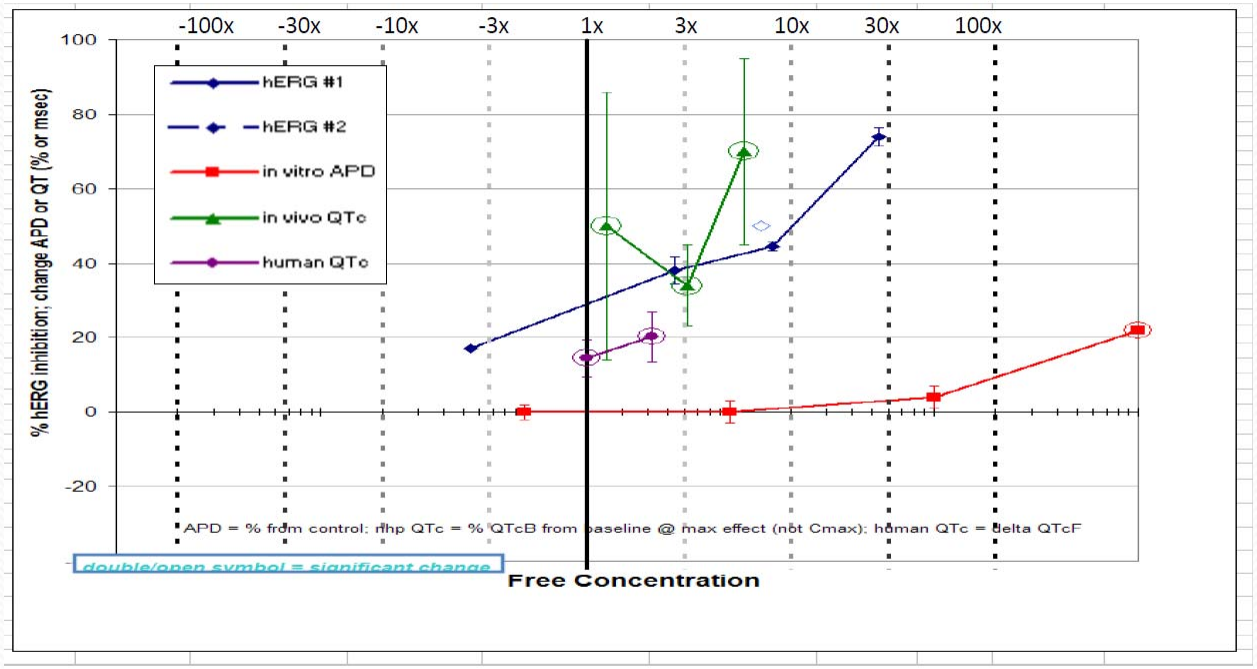
hERG	1X (n=13)	3X (n=13)	10X (n=13)	30x (n=12)
Specificity	0.40	0.40	0.25	0.0
Sensitivity	0.63	0.63	0.78	0.89
Concordance	0.54	0.54	0.62	0.67
APD	**1X (n=6)**	**3X (n=9)**	**10X (n=9)**	**30x (n=8)**
Specificity	0.67	0.80	0.60	0.60
Sensitivity	0.0	0.0	0.25	0.33
Concordance	0.33	0.44	0.44	0.50
QTc	**1X (n=8)**	**3X (n=15)**	**10X (n=13)**	**30x (n=10)**
Specificity	1.0	1.0	0.83	0.75
Sensitivity	1.0	0.57	0.71	0.83
Concordance	1.0	0.80	0.77	0.80
Integrated	**1X (n=18)**	**3X (n=20)**	**10X (n=19)**	**30x (n=18)**
Specificity	0.56	0.64	0.44	0.38
Sensitivity	0.56	0.67	0.90	0.90
Concordance	0.56	0.65	0.68	0.67

ILSI Health and Environmental Sciences Institute

- Encouraging concordance for the in vivo study to date
- The poorer specificity of hERG impacts the integrated assessment
- APD assays have a strong positive predictive value but low negative predictive value – been abandoned by many

In Vivo Study Quality an Issue

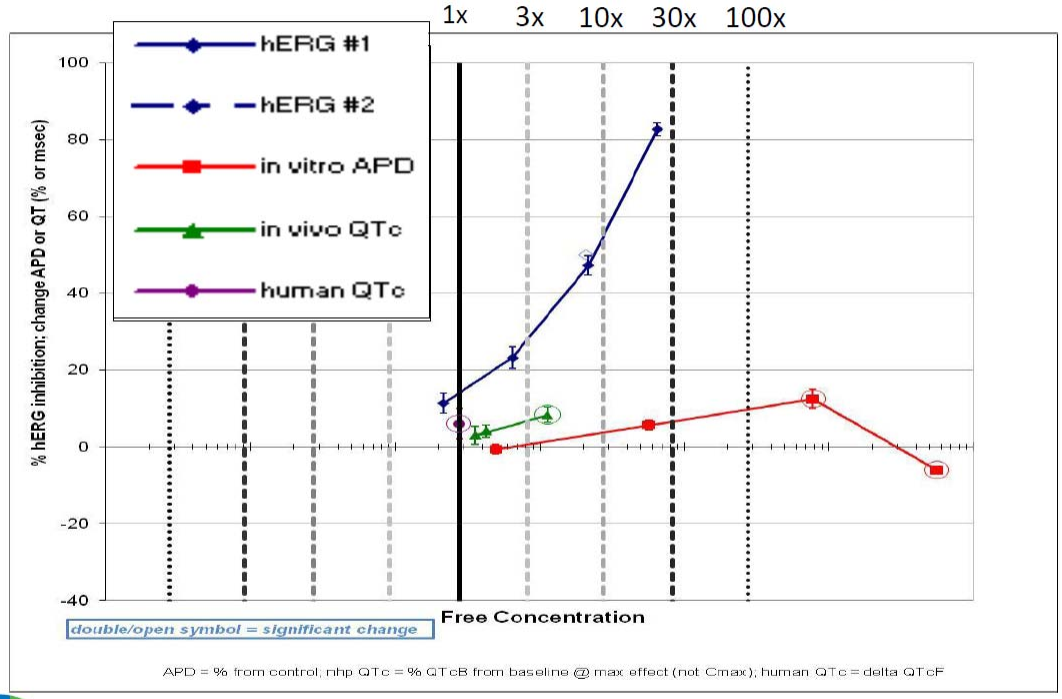
Concordant Positive Example 04



- Note the variability and shape of the in vivo QTc exposure-response relationship
- These changes were however all large and statistically significant

ILSI/HESI Data Included (Approach 3)

Example of positive QTc compound: Cisapride



- Clinical data: van Haarst et al., Clin Pharmacol Ther 1998;64:542-6

- Note the low variability in the ILSI/HESI data
- Sadly not representative of many submitted studies

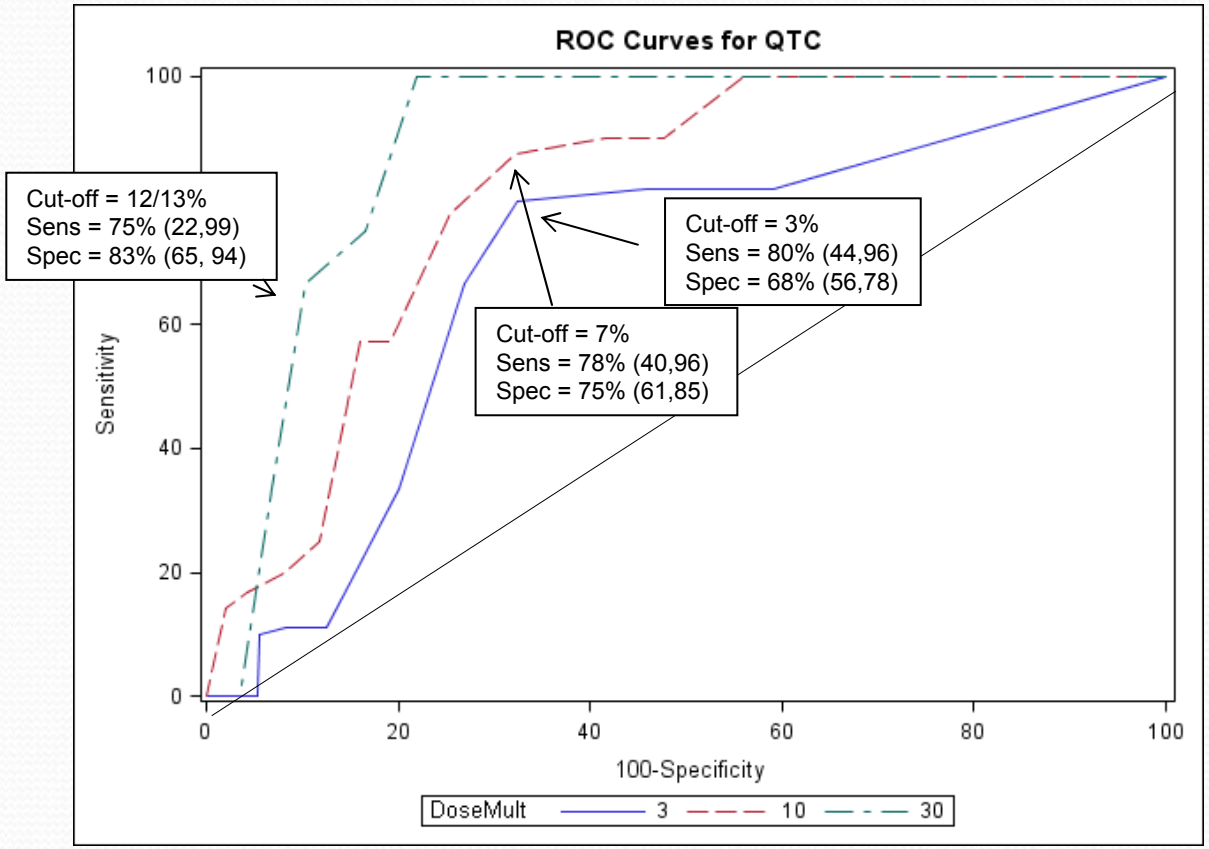
Animal Model Framework

1. Quantitative method to relate pre-clinical safety pharmacology data from dog telemetry (CVS), rodent Irwin/FOB (CNS) and rodent plethysmography (respiratory) models to Phase I clinical outcome in man
   - Valentin *et al*., 2009 JPTM 60 152-158

2. Retrospective analysis of small molecule compounds from 7 pharmaceutical companies under the umbrella of the Association of the British Pharmaceutical Industry (ABPI)
   - AstraZeneca, Amgen, Janssen, GSK, Pfizer, Eli Lilly, Novartis

3. Parameters from models will be mapped to a two dimensional framework
   - Confidence in the model
   - Confidence in the translation

Predicting QTc in FHD Studies



The dog telemetry model adequately predicts QTc changes in man based on the data analysis of the 114 compounds in the Animal Model Framework

How can Assay Sensitivity be Demonstrated in Early Clinical Studies?

- A more precise term for ‘Assay Sensitivity’ for experimental science is ‘assay validity’
- Positive controls for QT measurement were prescribed due to a lack of validation
- A positive control is unnecessary in a sufficiently valid study, and may worsen the predictive value of the study conclusions.

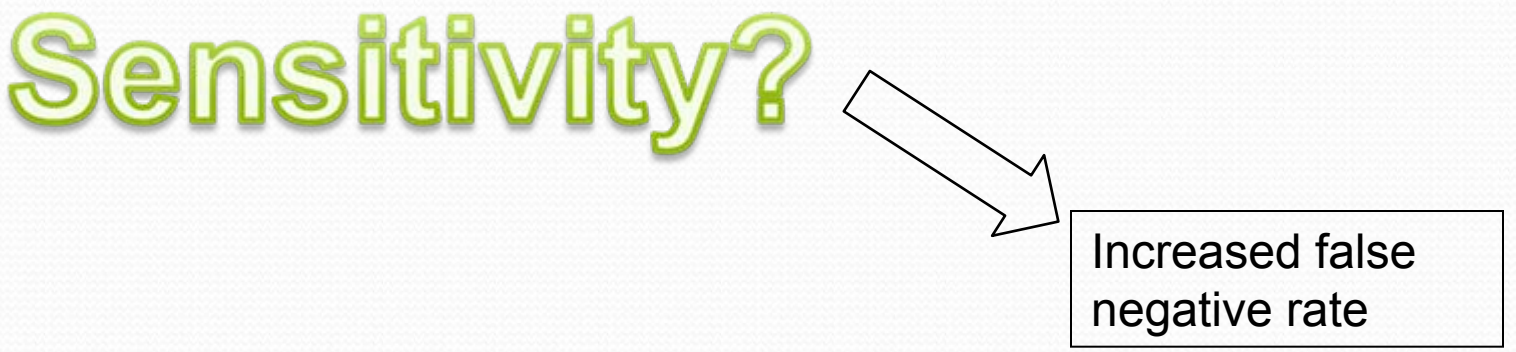
'Assay Sensitivity, Failed Clinical Trials, and the Conduct of Science'[4]

- "Subsequent, [negative] findings are then assumed to be the result of some failure of 'assay sensitivity' of the trial."
- "This reasoning, however, has the potential of distorting the scientific process, such that the adequacy of the trial is judged not by the design but, instead, by the results of the trial itself."

[4]Otto MW, Nierenberg AA: Psychother Psychosom 2002; 71:241–243

Data from the FDA IRT

- Based on 178 TQT studies we have reviewed, there were 9 studies which failed the assay test.
- Among those 9, most of them didn't show moxi time profile instead of failed 5 ms lower bound test.
- Many of these were over encapsulated (blinded) moxi



Why is QT special?

- Other biomarkers are important, have significant variability and not required to have a positive control to demonstrate lack of an effect:
  - LDL, HCT, LFTs, etc.
  - We consistently employed ‘tried and true’ methods of assay validation
  - QT shouldn’t be a special case
  - Sensitivity (false negative rate) is well controlled
  - Risk/benefit information is not well supported by positive control or additional TQT

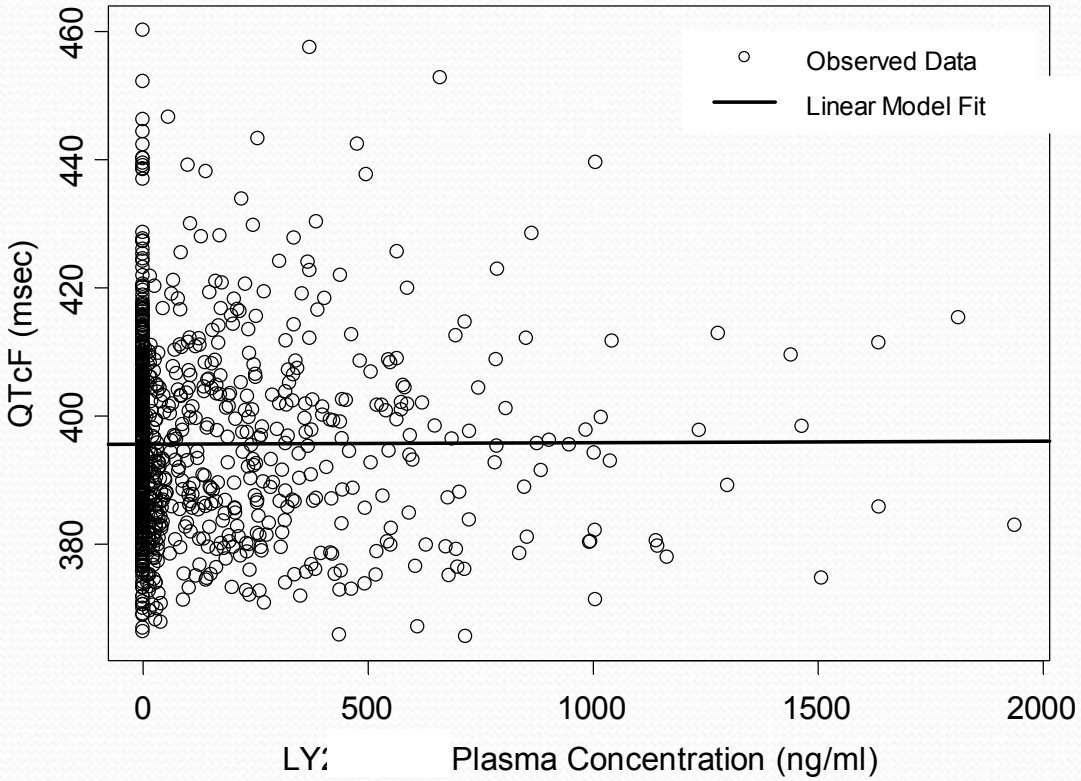
How can Assay Sensitivity be Demonstrated in Early Clinical Studies?

- Assay Validity has been demonstrated for many early phase clinical studies
  - Internal, Construct, External, Statistical conclusion validity have been established for QT studies
- Further 'validation' techniques
  - Malik method – variability, stability, reproducibility[3]
  - Retrospective power analysis[4]
    - A priori establishment of exclusion of 10msec
  - Empiric – past positive result

[3] Malik. ECG Assay Sensitivity Without Moxifloxacin. Oral presentation. DIA meeting. April 2010.

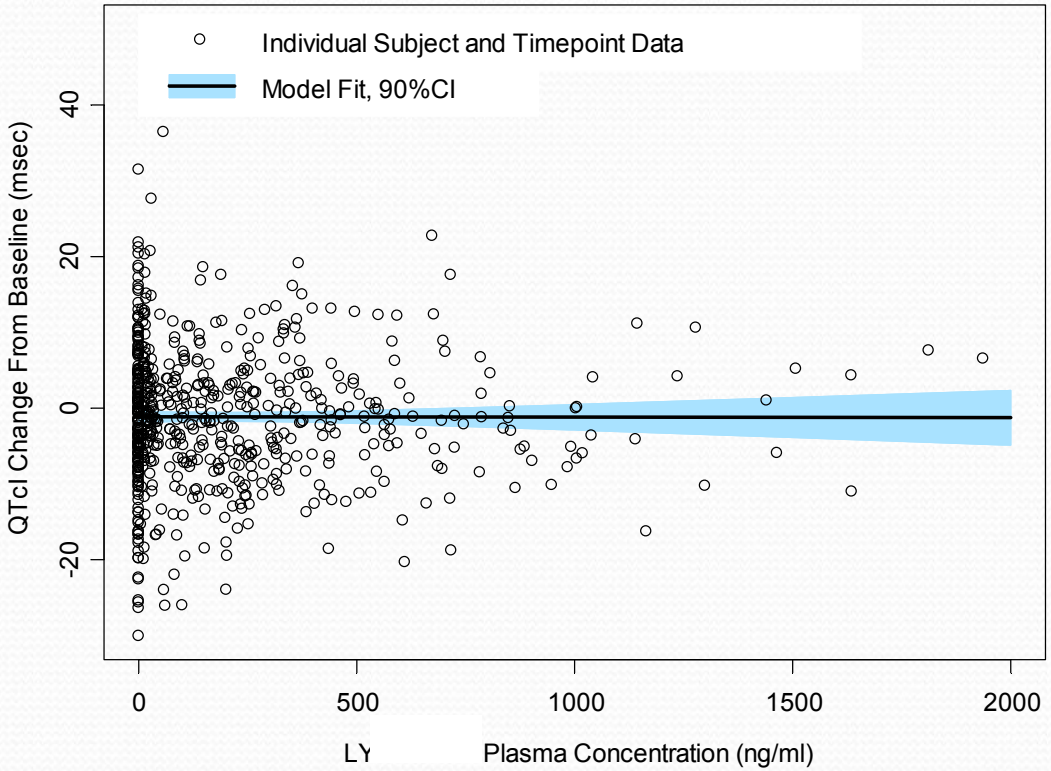
[4] Thomas, L. 1997 Retrospective power analysis. Conservation Biology. **11**, 276-280

Relationship Between LY Concentration and QTcF



- Slope of relationship between LY concentration and QTc = 0.0003 (90%CI: -0.0028 - 0.0034), p=0.891
  - Assuming above slope is the true mean relationship, a LY concentration of approximately 17000 ng/ml would be required to produce a mean QTc prolongation of 5 ms. This concentration is approximately 15-fold higher than the mean Cmax
- Since slope is positive but very small and the confidence interval includes zero it can be concluded that there is no clinically significant or statistically significant relationship between LY concentration and QTc

Relationship Between LY Concentration and QTcI Change from Baseline



Probability statements based on confidence intervals:

- **Concentration at which true mean change in QTcI is 95% likely to be less than 5ms: 3370 ng/ml**
- **At mean Cmax observed at 600mg (1300 ng/ml), probability that the true mean increase in QTcI is >5ms is <0.01%**
- **At 5x mean Cmax observed at 600mg (6500 ng/ml), probability that the true mean increase in QTcI is >5ms is 18.5%**

- Slope of relationship between LY concentration and QTcI change from baseline = -0.000055 (90%CI: -0.00205 - 0.00194), p=0.964
- Since slope is very small, negative, and the confidence interval includes zero it can be concluded that there is no clinically significant or statistically significant relationship between LY concentration and QTcI change from baseline

Methods of Establishment of Assay sensitivity:

- How do we know the slope isn't significantly greater than in your study?
- Or if the same experimental system demonstrates an approximately flat response –
- "[the positive control] is needed to ensure that the study is properly designed and conducted and able to detect small changes in QTc."
- **TQT STUDY IS NECESSARY ?**

Is a Thorough QTc Study Necessary? The Role of Modeling and Simulation in Evaluating the QTc Prolongation Potential of Drugs*

- Agreement of Pooled Phase I/II C-QT Models With Negative TQT Studies
  - "The C-QT analysis was dominated by a single phase I study that had serial triplicate ECGs taken during periods with substantial drug concentrations"
  - double-blind, randomized, parallel thorough QTc study evaluated AD1 at 3 mg and 10 mg (2× and 7× therapeutic dose), placebo, and moxi 400 mg for 7 days in 140 healthy participants (85 men and 55 women).

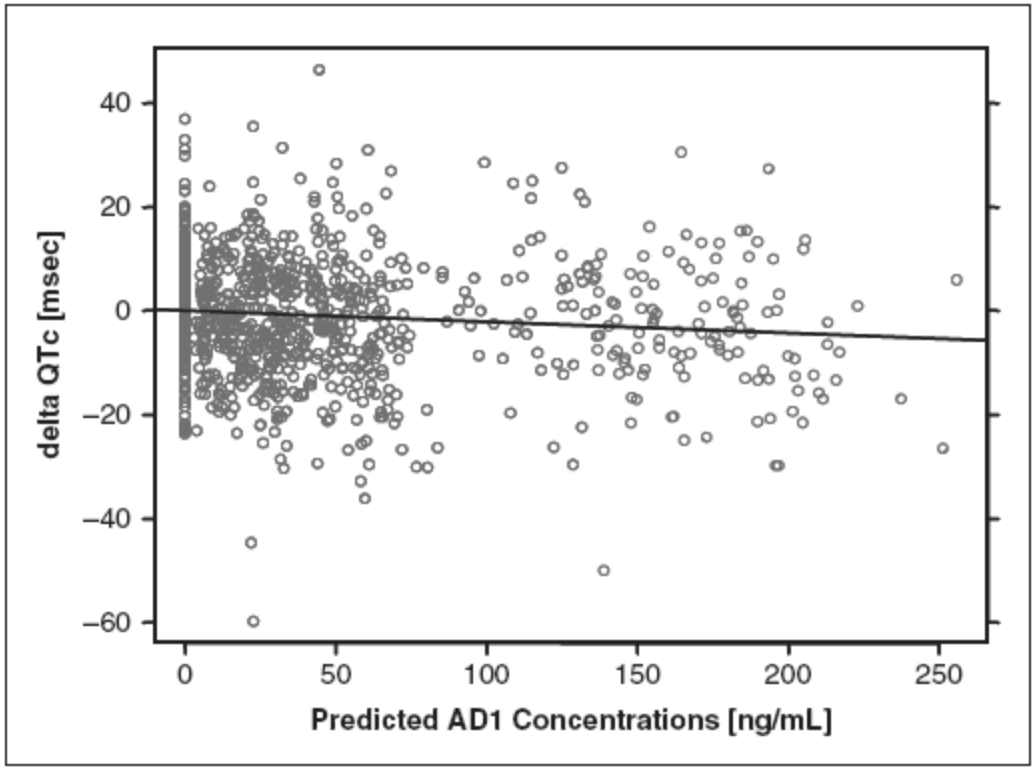


Figure 7. Negative slope indicated no potential for QTc prolongation.

*Rohatagi, Shashank, Carrothers, Timothy J., Kuwabara-Wagg, Jon, Khariton, Tatiana September 4, 2009 J Clin Pharmacol

Is a Thorough QTc Study Necessary? The Role of Modeling and Simulation in Evaluating the QTc Prolongation Potential of Drugs*

- Agreement of Pooled Phase I/II C-QT Models With Negative TQT Studies
  - AD1 3 mg and 10 mg were noninferior to placebo at every time point postdose ($\Delta\Delta$QTcF <5 ms with upper 95% CI <10 ms).

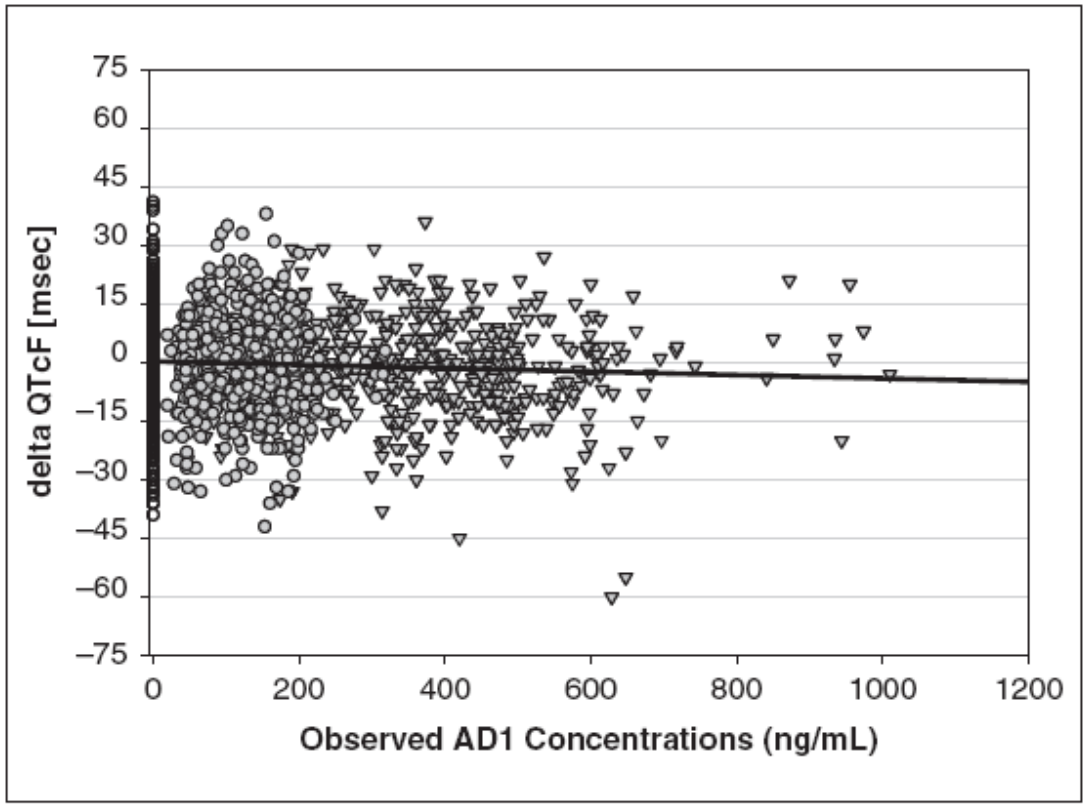


Figure 8. Negative slope observed in thorough QTc (TQT) study for AD1.

*Rohatagi, Shashank, Carrothers, Timothy J., Kuwabara-Wagg, Jon, Khariton, Tatiana September 4, 2009 J Clin Pharmacol

Is a Thorough QTc Study Necessary? The Role of Modeling and Simulation in Evaluating the QTc Prolongation Potential of Drugs*

- Agreement of Pooled Phase I/II C-QT Models With Negative TQT Studies
  - "it is reasonable to ask whether a TQT is necessary in the context of a well-constructed C-QT data set and analysis. Pooled single and multiple ascending-dose (SAD/MAD) data sets will span a dose range sufficient to cover and exceed the "supratherapeutic" dose of the TQT design."
  - "Two main arguments against this idea can be expected."
    - active control arm of moxifloxacin
    - lack of power - findings from the pooled analysis could well be a "false negative" due to insufficient power

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    - The first argument would maintain that without an active control arm of moxifloxacin, there would be no way to gauge the sensitivity of study participants to QT-prolonging drugs.
      - parallel-arm TQT studies are allowed, the issue of assay validation cannot be population sensitivity
    - "At the study level, standard procedures for ECG assessment and manual reading at a central laboratory can be implemented. In practice, manually read ECGs have shown stable results for moxifloxacin, so there should not be a concern for labs with experienced ECG readers. Alternatively, a small moxifloxacin comparative arm may be added in a SAD or MAD study."

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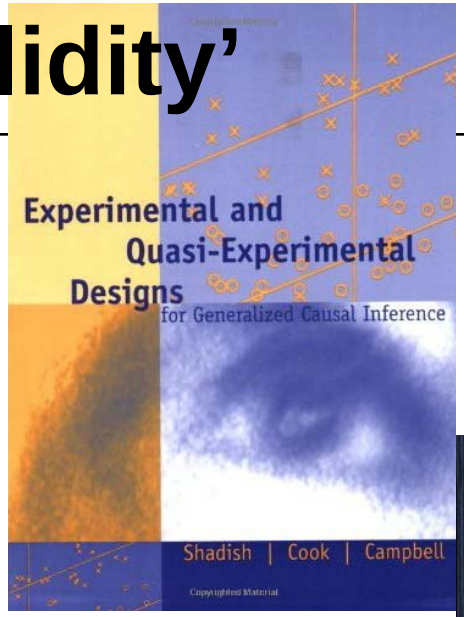
Methods of Establishment of Assay sensitivity:

- "In the case of a *negative or neutral* relationship between the drug concentration and QTc, a positive control is needed to assure assay sensitivity."
- **What is meant by 'Assay Sensitivity'?**

A more precise term for 'Assay Sensitivity' is 'Validity'

- Validity
  - Internal validity
  - Construct validity
  - External validity
  - Statistical conclusion validity*
    - Type I Error
    - Power (sensitivity)



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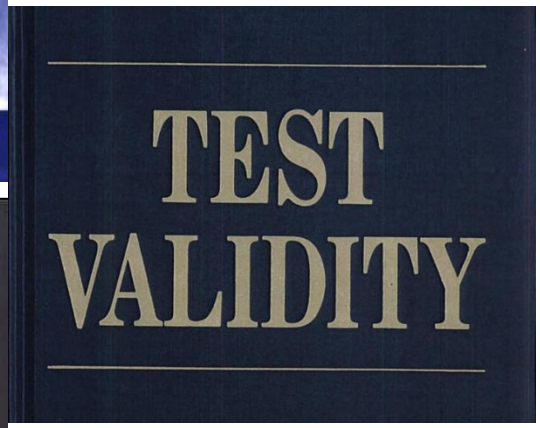
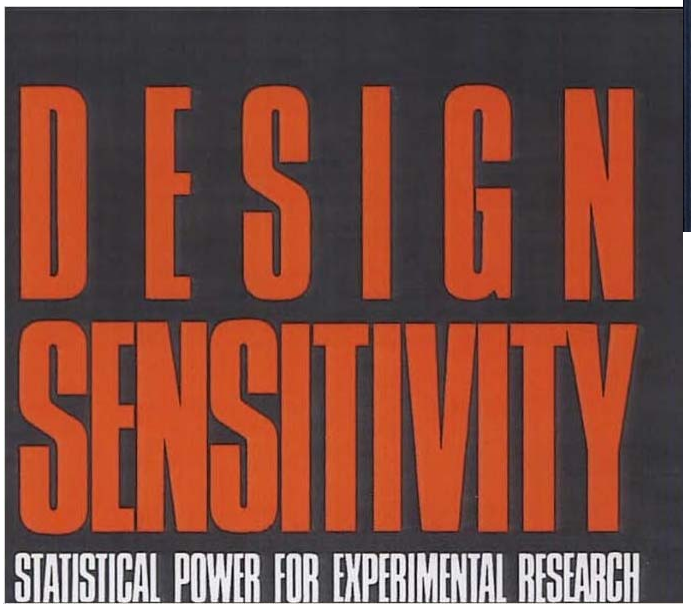


Test Validity: H. Wainer and H.J. Braun (Eds.). Hillsdale, NJ: Erlbaum.



Design sensitivity: statistical power for experimental research : Mark W. Lipsey, Sage Publications, Newbury Park, CA 1990

*Note: Some treat Type II error statistical conclusion validity as a separate topic called assay sensitivity.

Is a Thorough QTc Study Necessary? The Role of Modeling and Simulation in Evaluating the QTc Prolongation Potential of Drugs*

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- **Simulation Case Study**

  "Assuming a drug indeed prolongs the QTc interval, what are the chances that a C-QT model based on a multiple ascending-dose data set will not detect the effect?"

  - Compound with 5 msec prolongation (truth)
  - Each QTc measurement, including baseline, with intrasubject (ie, residual) error with a mean of 0 ms and a standard deviation of 15 ms.
  - MAD study, each arm with 10 participants, serial triplicate ECGs taken during periods with substantial drug concentrations.
  - 5000 replicates of the trial were simulated

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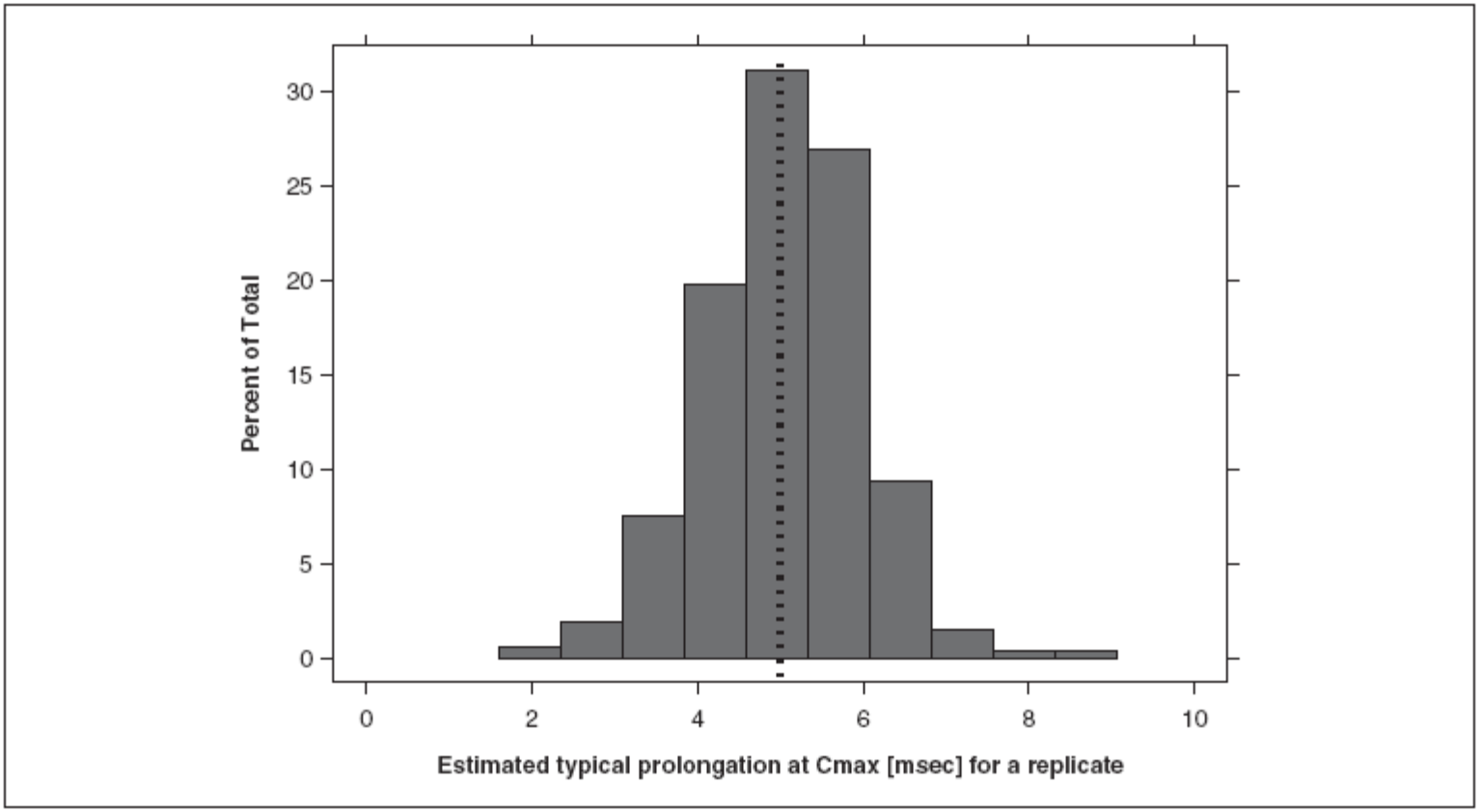

Figure 11. Distribution of estimated prolongation at typical C_{max} based on modeled C-QT slope in the "5-ms positive" exercise. Note that the dotted line corresponds to 5 ms "true state of world."

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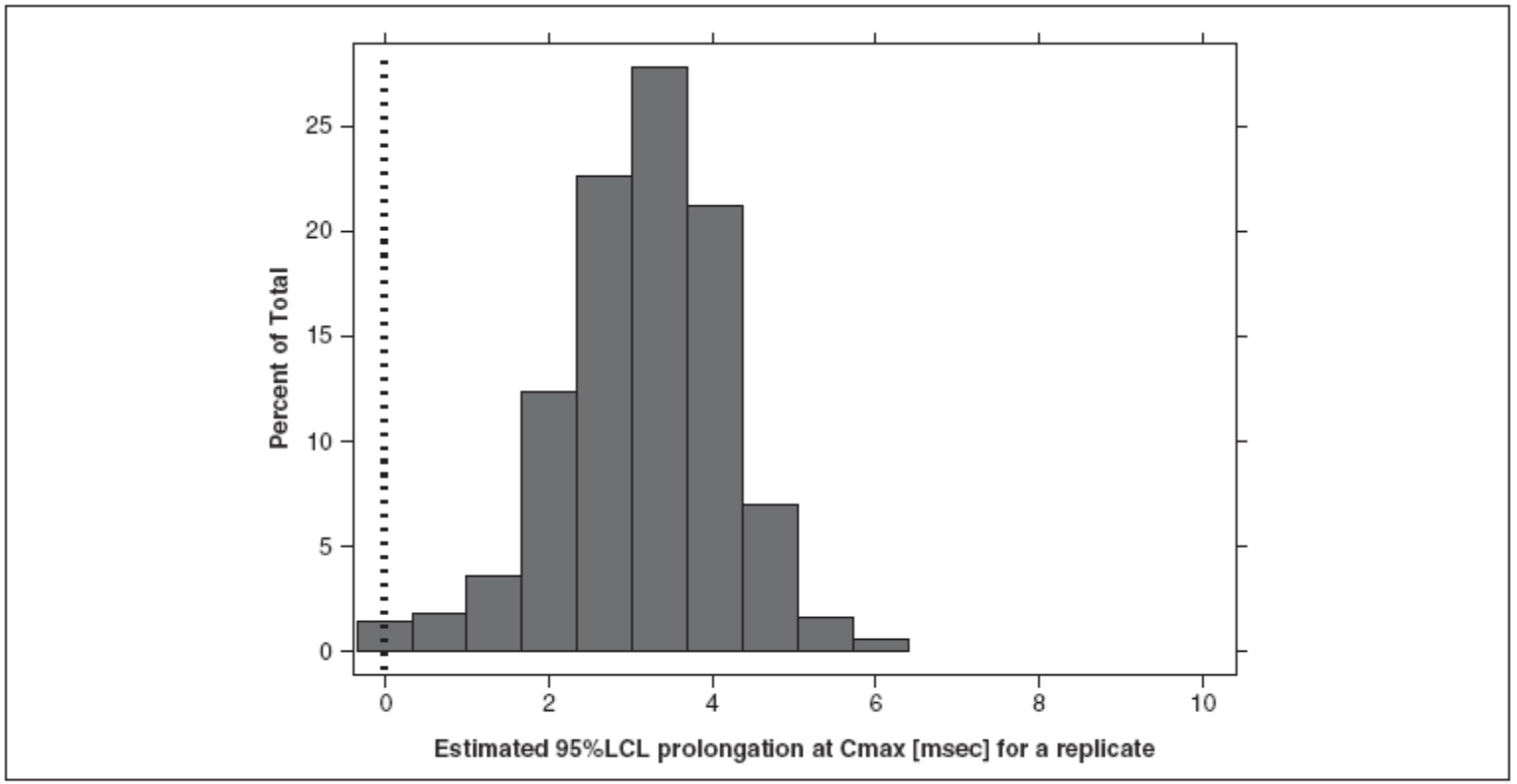

Figure 12. Distribution of 95% lower confidence limit (LCL) prolongation at typical C_{max} based on modeled C-QT slope in the "5-ms positive" exercise.

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- "even in the case where the C-QT model data set consists of only a multiple ascending-dose study with 40 participants, the C-QT model estimated a statistically significant, positive slope 99% of the time"
- FN rate < 1%.
- "if a C-QT model based on a data set of similar or greater richness and size estimates a slope nonsuperior to 0, the results can be taken with confidence that a regulatory-meaningful effect does not exist at the dose studied"

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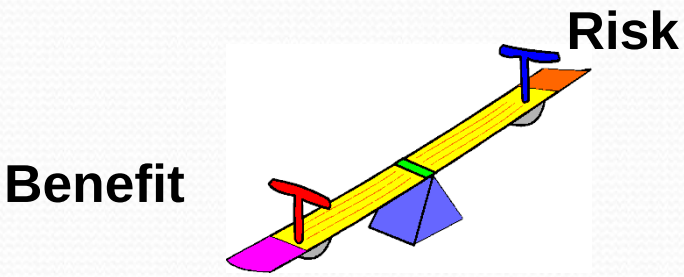
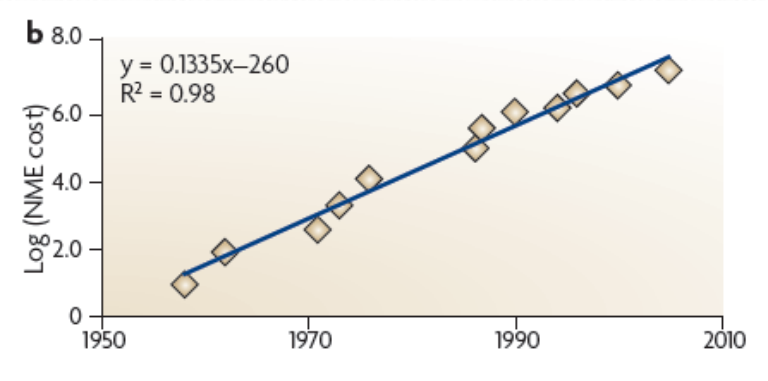
Comments about the positive control

- "the specter of the positive control helps assure good trial performance"
- "... the trials became larger and more carefully conducted as a result of insisting upon the positive control."
- "By having an operational assessment of study quality, [the positive control] frees sponsors to explore more efficient study designs and measurement technology."





B. Munos, *Nature Reviews Drug Discovery* Vol. **8**, Dec 2009, 959 - 968