In Silico Models for Screening New Drugs for QT Prolongation Potential using Human Clinical Trial Data

OpenTox USA 2013
Innovation in Predictive Toxicology
October 30, 2013

Luis G. Valerio, Jr., Ph.D.
U.S. FDA, Center for Drug Evaluation and Research
Office of Pharmaceutical Science

Kevin P. Cross, Ph.D.
Leadscope, Inc.

Regulatory Issue

- Drug-induced prolongation of the electrocardiographic QT interval is a cardiovascular safety consideration of paramount importance.
  - The QT interval on ECG is a measure of ventricular depolarization and subsequent repolarization.
  - It may be associated with ventricular tachycardia torsade de pointes (TdP)
  - Sudden cardiac death
- Nonclinical safety assays of new drugs to induce QT interval effects are indispensable (ICH S7B).
- However, prediction of potential TdP in humans remains a challenge
  - Only a proportion of QT prolongers induce TdP
  - Some hERG blockers are not proarrhythmic

Project Goal

- Build an *in silico* proarrhythmia assessment tool based on human data to detect, assess, and value proarrhythmic liability of new drugs to support cardiac drug safety assessments.

- Clinical Decision Support tool
  - A Qualitative Assessment for Concerns
    - ✓ Forecast QT/QTc and TdP liability
    - ✓ Structural alert
    - ✓ Chemically characterize CDER's thorough QT clinical studies (TQT)
    - ✓ Enable search for analogous drugs

Focus on

- Quality and innovation
  - Clinically relevant data to detect proarrhythmic effects
    - ✓ Evidence-based and regulatory concurrence of study data
  - Harnessing of prediction technologies at CDER
  - Data integration and whole process understanding of the model
  - Consistent with FDA's Strategic Plan for Advancing Regulatory Science
    - ✓ Reduce drug and development costs
    - ✓ Modernize toxicology to enhance product safety

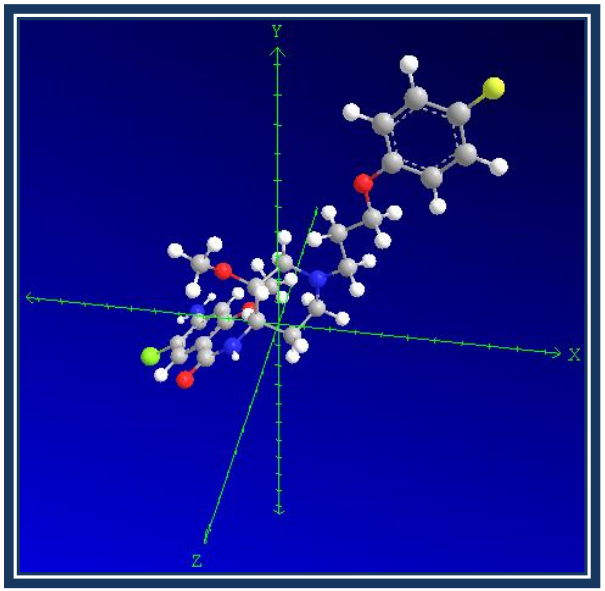
      "Use and develop computational methods and *in silico* (computerized) models"

Key Strategy

- Predictive model must be
  - ✓ Hypothesis-based
  - ✓ Based on high quality empirical clinical evidence
  - ✓ Probabilistic prediction of risk
  - ✓ Within the needed degree of precision
  - ✓ Meet the design space of new drugs based on chemical characteristics

Innovative Approach

- Computerized prediction models of drug molecular structure



INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

THE CLINICAL EVALUATION OF QT/QTC INTERVAL PROLONGATION AND PROARRHYTHMIC POTENTIAL FOR NON-ANTIARRHYTHMIC DRUGS

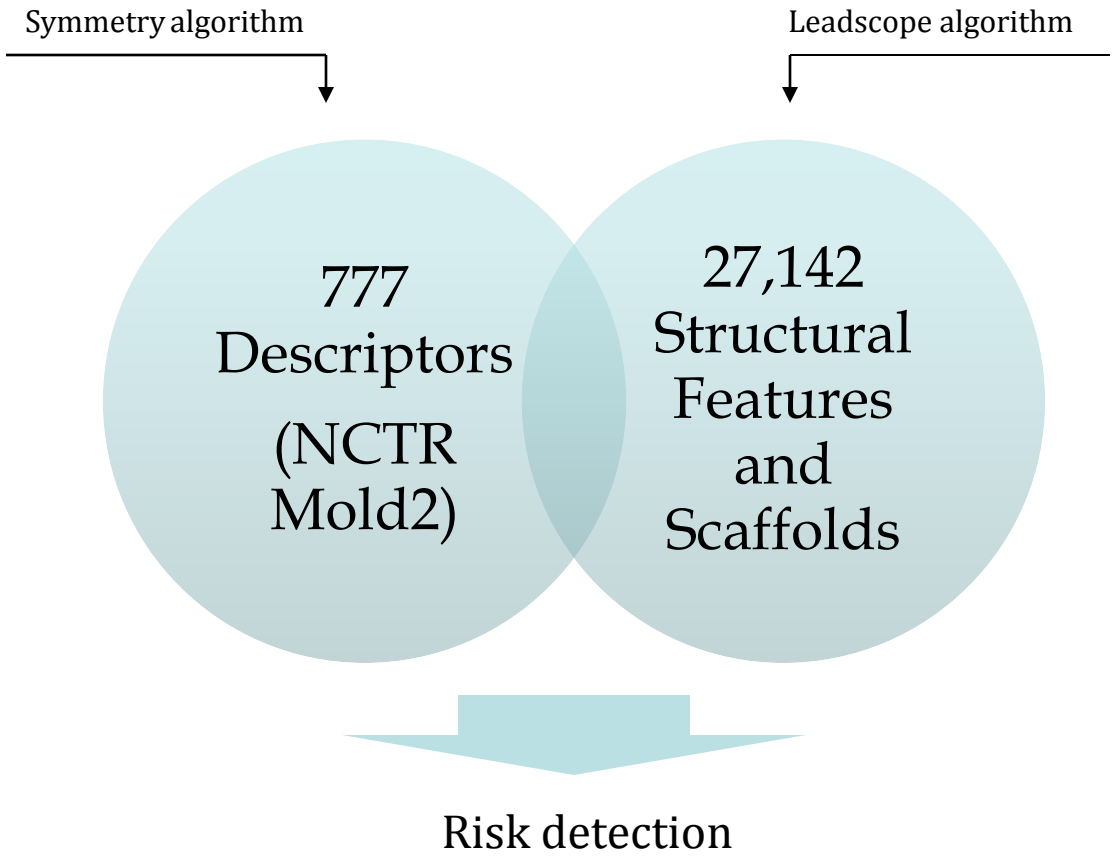
E14

Current *Step 4* version
dated 12 May 2005

- Regulatory clinical guidance. Risk-based

Methodology: Tool Selection

Quantitative Structure-Activity Relationships



Data Standards

- Definition and criteria of positive QT/QTc drugs

Model Type	
In-House QT Model	**High Risk Torsade de Pointes Model**
Drug exceeded the threshold level of regulatory concern in a Thorough QT study as delineated by ICH E14 guidance where the effect was around 5 ms as evidenced by an upper bound of the 90% confidence interval around the mean effect on QTc > 10 ms. Metabolites of prodrugs with significant exposure-response relationship on QT/QTc were included when possible. Or	Positive QT/QTc drugs with upper bound 90% or 95% CI of mean QT/QTc interval prolongation > 20 ms at the therapeutic dose. Or
The upper bound 90% CI of mean ΔΔQTc or ΔΔQTc interval prolongation for the drug was > 10 ms at therapeutic dose level or supratherapeutic dose level.	Positive QT/QTc drugs with upper bound 90% or 95% CI of mean QT/QTc interval prolongation > 20 ms at the supratherapeutic (ST) dose and there was drug-related TdP incidence; or sudden death observed either in the postmarking cases or during the TQT or QT studies, or if the ST dose is = or < than 3X the therapeutic dose and a positive trend in concentration response was seen. Or
	Drug is listed by Arizona CERT Advisory board for risk of causing Torsade de Pointes

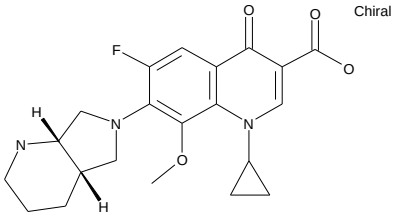
Data Standards

- Definition and criteria of negative QT/QTc drugs

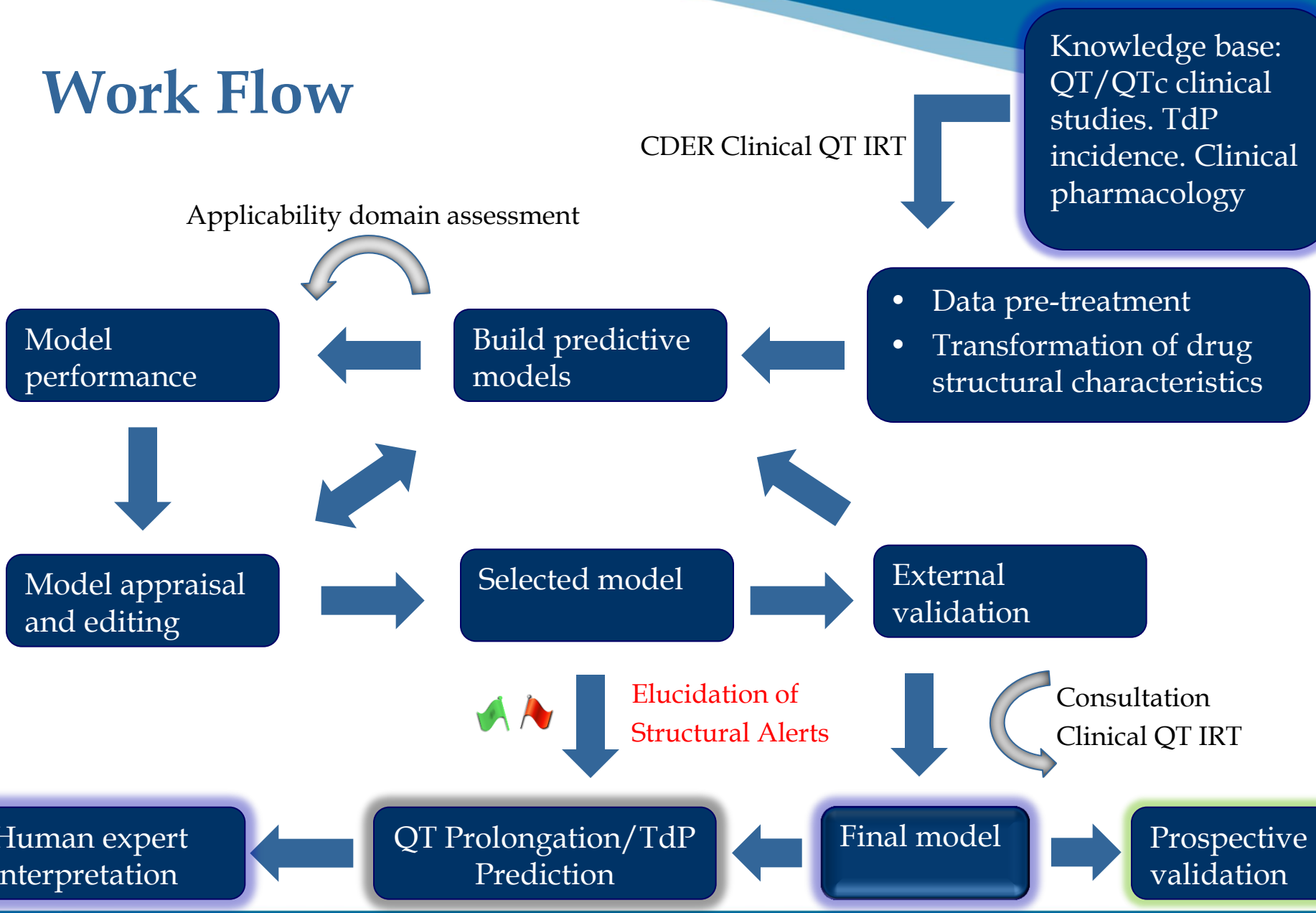
Definition and Criteria
The "negative QT/QTc drug" is defined as a drug, or a compound submitted as a potential drug, that has been investigated in a "thorough QT" (TQT) or a QT study, in which no apparent QT/QTc interval prolongation effects and no significant exposure-response relationship have been observed.
The upper bound of the 90% confidence interval around the mean of ΔΔQTc is below 10 ms.
No statistically significant exposure-response (concentration-QTc response) relationship was observed.
Assay sensitivity had to be established.

- Drug molecular structures

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health
Substance Registration System - Unique Ingredient Identifier (UNII)

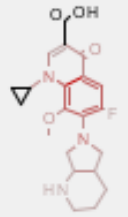


Work Flow


Knowledge base: QT/QTc clinical studies. TdP incidence. Clinical pharmacology
CDER Clinical QT IRT
Applicability domain assessment
Data pre-treatment
Transformation of drug structural characteristics
Build predictive models
Model performance
Model appraisal and editing
Selected model
External validation
Elucidation of Structural Alerts
Consultation Clinical QT IRT
Human expert interpretation
QT Prolongation/TdP Prediction
Final model
Prospective validation

Model Decision Explained

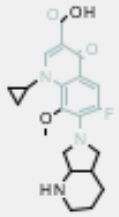
Positive Features



Feature Contribution: 0.9979

Select Atoms For Contribution

Negative Features



Feature Contribution: -0.1052

Select Atoms For Contribution

Model: In-House QT Prolongation (ver1)

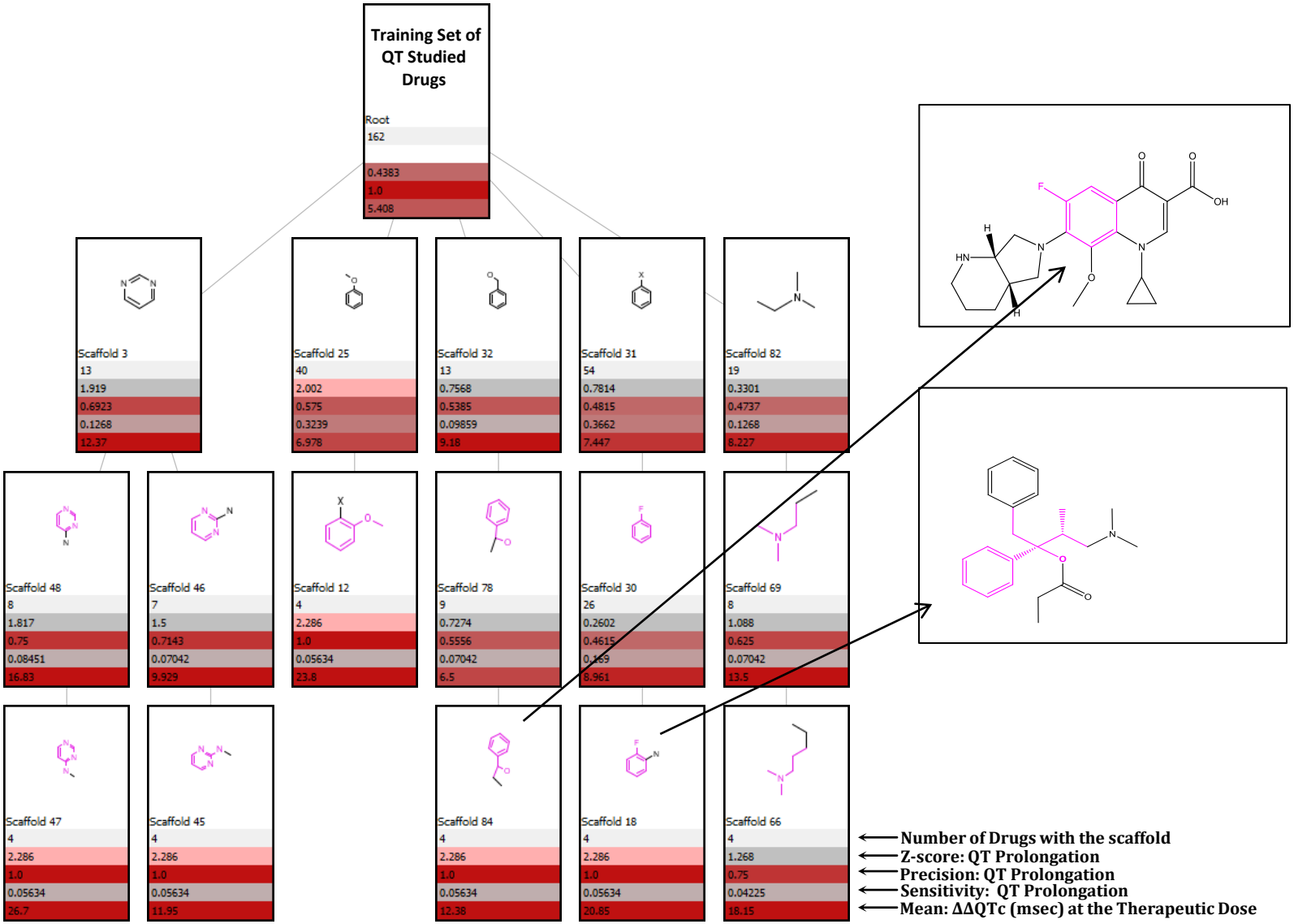
# of Training Structures: 162
# of Features: 23 of 184 total
# of Property Descriptors: 8

Predicted Value: 0.994
% Feature Contribution: 89.82%
% Property Contribution: 10.18%

Generate Report... | Add/Remove Column

	%Partial Property	Partial Property	Total Weight	Actual Values
	13.47	0.1339	0.132	

Methodology: Features and Scaffolds



Assessment of the Predictive Value of an *In Silico* QT/QTc Prolongation Model

External validation

Leadscope

Algorithm: Partial Logistic Regression.
Enriched with mechanistic information *post-hoc* (hERG inhibitors < 1 μM, and non-inhibitors)

Sensitivity	Specificity	Concordance	False Positive Rate	False Negative Rate	Positive Predictivity	Negative Predictivity	Cohen's Kappa
86%	78%	82%	22%	14%	82%	82%	0.637

Drug Coverage of the Model	
49 Drugs in the External validation test	80%
1,551 Marketed Drugs Drugs@FDA, NDC, Orange book	56%

Drugs withdrawn from the market	Model Prediction for QT/QTc Prolongation
Terfenadine	0.793 probability of being positive
Cisapride	0.776 probability of being positive

100 Y-Scrambled Model Results

	Overall Original	Overall Scrambled	Delta
Concordance	77.4	54.6	22.8
Sensitivity	82.9	27.1	55.8
Specificity	73.8	70.8	3.0
Positive Predictivity	66.7	35.4	31.3
Negative Predictivity	87.3	62.2	25.1

Assessment of the Predictive Value of an *In Silico* TdP Model

Cross-validation

Predictive Technology and Algorithm	Sensitivity	Specificity	Concordance	False Positive Rate	False Negative Rate	Positive Predictivity	Negative Predictivity	Cohen's Kappa
Leadscope Combined probabilistic and similarity	82%	90%	88%	10%	18%	80%	91%	0.720

Coverage of the Model	
1,551 Marketed Drugs-Drugs@FDA, NDC, Orange book	47%

	Overall Original	Overall Scrambled	Delta
Concordance	87.6	57.9	29.7
Sensitivity	82.2	25.9	56.3
Specificity	90.2	73.6	16.6
Positive Predictivity	80.4	32.4	48.0
Negative Predictivity	91.2	67.0	24.2

Assessment of the Predictive Value of an *In Silico* QT/QTc Prolongation Model

External validation

Predictive Technology and Algorithm	Sensitivity	Specificity	Concordance	False Positive Rate	False Negative Rate	Positive Predictivity	Negative Predictivity	Cohen's Kappa
Symmetry Combined probabilistic and similarity	74%	79%	77%	21%	26%	74%	79%	0.531

Coverage of the Model	
70 Drugs of the External validation test	98%
1,475 Marketed Drugs-Drugs@FDA, NDC, Orange book	97%

Drugs withdrawn from the market	Model Prediction for QT/QTc Prolongation
Terfenadine	0.510 probability of being positive
Cisapride	0.650 probability of being positive

Assessment of the Predictive Value of an *In Silico* TdP Model

Cross-validation

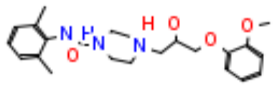
Symmetry Algorithm: Combined probabilistic and similarity							
Sensitivity	Specificity	Concordance	False Positive Rate	False Negative Rate	Positive Predictivity	Negative Predictivity	Cohen's Kappa
87%	92%	91%	8%	13%	85%	93%	0.786

Drug Coverage of the Model	
1,475 Marketed Drugs Drugs@FDA, NDC, Orange book	96%

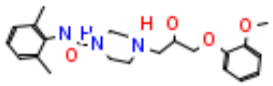
Computer Model Predictions

Symmetry

QT/QTc Model

	Molecule ID (Substance ID)	Score (prob. of positive)	Std. Dist. AD+	Std. Dist. AD–	Prediction Result
	Ranolazine	0.6	0.28	0.285	+

TdP Model

	Molecule ID (Substance ID)	Score (prob. of positive)	Std. Dist. AD+	Std. Dist. AD–	Prediction Result
	Ranolazine	0	0.128	0.199	–

Risk Assessment Implications

- Aid in data interpretation: equivocal, "weak positive" results, or conflicting evidence.
- Help prioritize the level of risk for decision-making.
  - Add information to the safety profile.
  - In special cases (*e.g.*, requests not to perform a TQT), pre-INDs, or considering a protocol.
- Alternative predictive tool to integrate with non-clinical mechanistic testing.

Technology Transfer

- Transfer of knowledge on product safety between regulatory and drug development to continually improve detection of torsadogenic drugs.

- Shares chemical knowledge on "safe" drug structural features to help ensure a safe drug design space.

- Helps identify "promiscuous" structural properties (fragments and descriptors) associated with TdP.

Impact to CDER and Outcomes

- Investigative safety science based on CDER in-house clinical (TQT) study data.
- Well designed and understood model. Provides structure-based explanation (alerts).
- Prospective validation testing in progress.
- Learning process on potential to influence decision-making on pre-INDs and TQT protocols.
- Publication

Valerio LG Jr, Balakrishnan S, Fiszman ML, Kozeli D, Li M, Moghaddam S, Sadrieh N. DEVELOPMENT OF CARDIAC SAFETY TRANSLATIONAL TOOLS FOR QT PROLONGATION AND TORSADE DE POINTES. *Expert Opinion on Drug Metabolism and Toxicology* Jul 2013, Vol. 9, No. 7:801-815.

Acknowledgements

- OPS/IO and OND/DCARP Clinical QT IRT

Funding and Technology Transfer

- FDA Critical Path Initiative
- Oak Ridge Institute for Science and Education (ORISE) fellow program
- FDA Research Collaboration Agreements
  - Prous Institute for Biomedical Research (Barcelona, Spain)
  - Leadscope Inc., (Columbus, OH)

Thank you

References

FDA Strategic Priorities 2011-2015 Responding to the Public Health Challenges of the 21st Century. Department of Health and Human Services, U.S. Food and Drug Administration, Silver Spring, MD, USA; 2011. Available from: http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm227527.htm

Hong, H., Xie, Q., Ge, W., Qian, F., Fang, F., Shi, L., Su, Z., Perkins, R., and Tong, W. 2008. Mold^2, molecular descriptors from 2D structures for chemoinformatics and toxicoinformatics. *Journal of Chemical Information and Modeling*. 48(7):1337–1344

ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, CDER/CBER; Rockville, MD 2005.

ICH S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals, Guidance for Industry, U.S. Department of Health and Human Services, Food and Drug Administration, CDER/CBER; Rockville, MD 2005.