CiPA In Silico Breakout Session

Discussion Points

Considerations for Implementing the Proposed CiPA Model (CiPAORdv1.0)

- IC50 vs hERG dynamic
  - Dynamic seems necessary
  - We need more labs to test dynamic and IC50s to look at effect of lab-lab variation.
- User friendly interface?
- Training data are available
- Validation data coming soon with paper

General Principles for Qualifying New Models Under CiPA

- Principle 1 (from ICH M7): A defined endpoint
  - ➢All models use the same TdP endpoint (CiPA 28 drugs and 3 categories)?
  - ➢Leave room for improved risk markers and more drugs
  - ➢But any improvements should re-run existing data/models through to any new risk endpoint

General Principles for Qualifying New Models Under CiPA

- Principle 2 (from ICH M7): An ambiguous algorithm
  - Should we require models under CiPA to be all open source? Or at least give enough public information for others to re-implement the model?

  - Yes!

General Principles for Qualifying New Models Under CiPA

- Principle 3 (from ICH M7): A defined domain of applicability
  - Under CiPA, a defined applicability domain (AD) means all drugs need to be assayed (experimentally and computationally) exactly the same way, and a new drug can only be compared to classification thresholds established by drugs from the same AD
  - Should we require that for a given model all compounds need to be assayed using unified experimental conditions (protocols etc) to ensure they are within the same AD?
  - Due to lab-to-lab variability, should we ask each lab to establish its own AD for a given model (assay a series of drugs and re-establish classification thresholds for each lab)?
  - After lab-specific AD is established, when a lab submits a new compound's data for regulatory consideration, should we require the lab submits 1-2 positive control drugs per channel to prove the new submission is still within the AD of the same lab?

General Principles for Qualifying New Models Under CiPA

- Principle 4 (from ICH M7): Appropriate measures of goodness-of–fit, robustness and predictivity
  - ➢should we require all new models under CiPA to be developed/validated using a stringent, clinical trial-like approach like CiPAORdv1.0 (training using 12 drugs – publication and freezing the model – validating using 16 drugs)?

General Principles for Qualifying New Models Under CiPA

- Principle 5 (from ICH M7): A mechanistic interpretation
  - If two models show similar prediction accuracy on TdP risk during validation, but different accuracy in predicting physiology (for instance, one is a physiological model while the other is a pure statistical model, or both are physiological model but one of them recapitulates experimentally recorded hERG currents or AP prolongation more accurately), should we have more confidence in the TdP prediction from the more “physiological” model?

General Principles for Qualifying New Models Under CiPA

- Principle 6: Uncertainty quantification
  - should we require all TdP risk prediction models under the CiPA paradigm to have some form of uncertainty quantification to characterize the uncertainty from experimental data and other sources?

Priorities for Future Improvements

- Alternative/improved hERG kinetics (both baseline and drug binding kinetics)
- Testing and improvement of other ion channel kinetics in the ORd model
- Tailoring of model for different subpopulations age, sex – can we validate at present?
- Validation of stem-cell derived myocyte model predictions (tailoring to different companies' cells?) to assist in interpretation of iPSC-CM experimental results?
  - Models for other in vivo safety test species to assist safety pharmacologists as compounds progress?
- Work to assist with the Phase I ECG study – simulating expected ECG biomarkers (J-Tpeak etc.) and assisting with their interpretation.