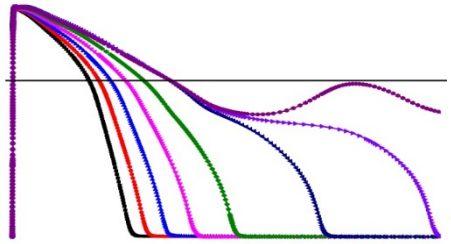
Overview: Scientific approaches, planned outputs & how data will be used

Comprehensive In Vitro Proarrhythmia Assay (CIPA) Update Meeting

Rockville, MD

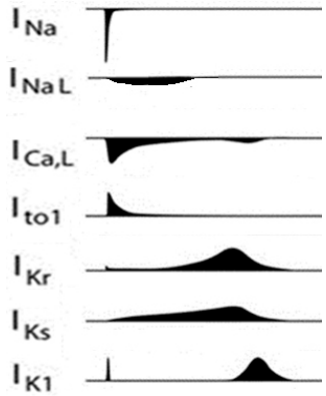
6 December 2016

$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



Ion Channel → *In Silico* Workflow in CiPA

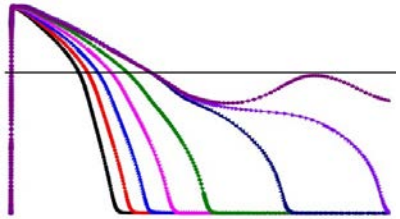
Drug Effects on Multiple Human Cardiac Currents



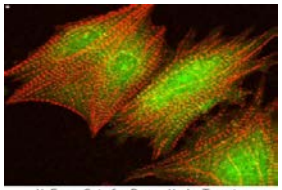
modified from Hoekstra et al., 2012

***In Silico* Reconstruction Human Ventricular Cellular Electrophysiology**

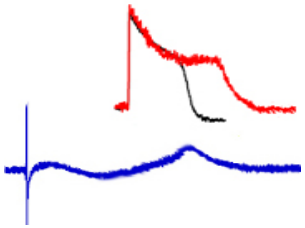
$$I_{stim} = C\frac{dV_m}{dt} + I_m$$



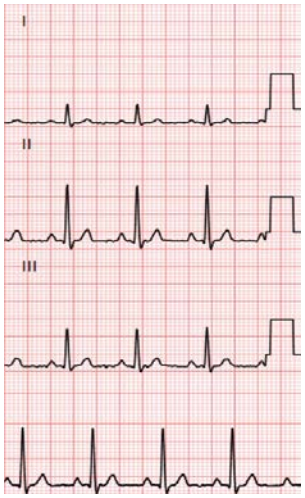
***In Vitro* Effects Human Stem-Cell Derived Ventricular Myocytes**



McEwen Cntr for Regen Med., Toronto



Clinical Evaluation Unanticipated EP Effects



a) **Obtain patch clamp data on human cardiac ion channels contributing to TdP risk**
b) **Use these data as inputs to an *in silico* model of the human ventricular myocyte**
c) **Run simulations and calculate a metric that accurately classifies the level of TdP risk**
d) **Use results to inform a regulatory decision on clinical drug safety (TdP)**

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Key Requirements

- **For generating ion channel data**
  - Assays should be compatible with current industry “best practices”
  - Protocols should not be overly complex and/or resource intensive
  - Methods should provide data consistent across labs, drugs and studies
- **For *in silico* model development:**
  - Keep it simple and make all assumptions transparent
  - Preserve an immediate and direct relationship to experimentally derived and verifiable data sets (O’Hara-Rudy = ”gold standard”)
  - Make the model and supporting data sets available as a community resource, without a need for specialized hardware or software
- **For development of an *in silico* TdP risk metric:**
  - Mechanistic (vs. phenotypic: QT prolongation alone is not predictive)
  - Quantitative and continuous: should span a wide enough range of values to clearly separate drugs with different levels of clinical TdP risk

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Initial Framework: Many Points to Consider

Ion Channel Pharmacology

- Which cardiac channels?
- Which assay systems and experimental conditions?
- What types of data (IC50, dynamic block)?
- Standardized patch clamp protocols?
- Data quality criteria? GLP?

Raw data → Model parameters ?

O'Hara Rudy Model

- Can base model performance be improved?
- How should drug-channel interactions be represented?
- What is needed to enable use of patch clamp data as inputs?
- Is there a need for multiple simulation protocols?
- How should the model & documentation be made available?

Simulations → Proarrhythmia signal(s) ?

Clinical Risk Metric

- Mechanism-based
- Continuous scale (not binary)
- Rank ordered comparisons (vs. reference drugs)
- Acceptable for regulatory decision making
- What drug concentrations?

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Translational Questions Raised

- **Since we are evaluating drug effects on native adult human cardiac channels, should the channels used in assays exhibit the gating kinetics and pharmacology of the native channels?**
  - Effects of subunits expressed?
  - Effects of experimental solutions?
  - Effects of temperature?
  - Other factors?
- **Can the *in silico* model correct for any discrepancies?**
- **Will any issues continue to be confounds?**
  - In the development phase using manual patch clamp methods?
  - In the implementation phase using automated patch clamping?
- **What impact will any residual confounds have on the regulatory prediction of clinical TdP risk?**

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Four Stage *In Silico* Development Plan

- **Exploratory phase**: assess the contribution of individual channels using “virtual” concentration-response experiments
- **Calibration phase**: assess model performance and modify model as required; identify candidate metrics that can classify TdP risk using a test set of 12 drugs with well characterized clinical profiles
- **Validation phase**: assess model performance, define boundary conditions using a validation set of 16 drugs with well characterized clinical profiles
- **Final “break the model” phase**: confirm boundary conditions for *in silico* model use by evaluating a test set of drugs/chemicals (submitted by external groups) that have sufficient contextual data to define the level of TdP risk

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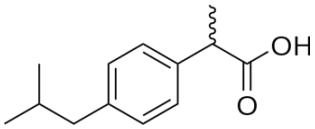
A Wide Range of *In Silico* Models Are Currently Being Used in Drug Development

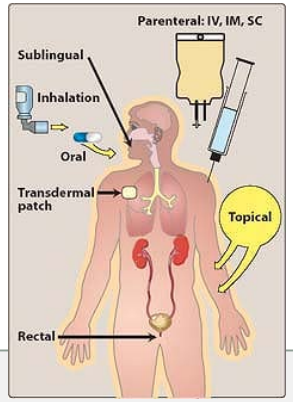
CHEMISTRY MODELS



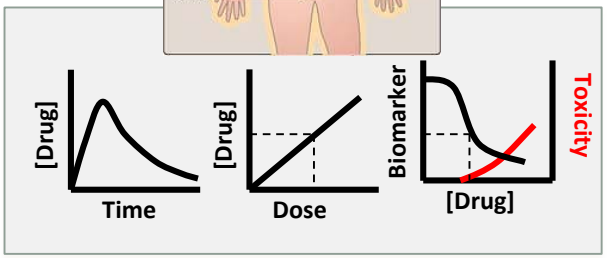
Docking models
Structure-activity relationships
Formulation
Manufacturing

EXPOSURE MODELS

ADME
IVIVC



PK
PBPK
PKPD



BIOLOGY MODELS

Disease
Pharmacology
Toxicology

Gene
Proteins
Pathways
Cells
Organs
Patients
Populations

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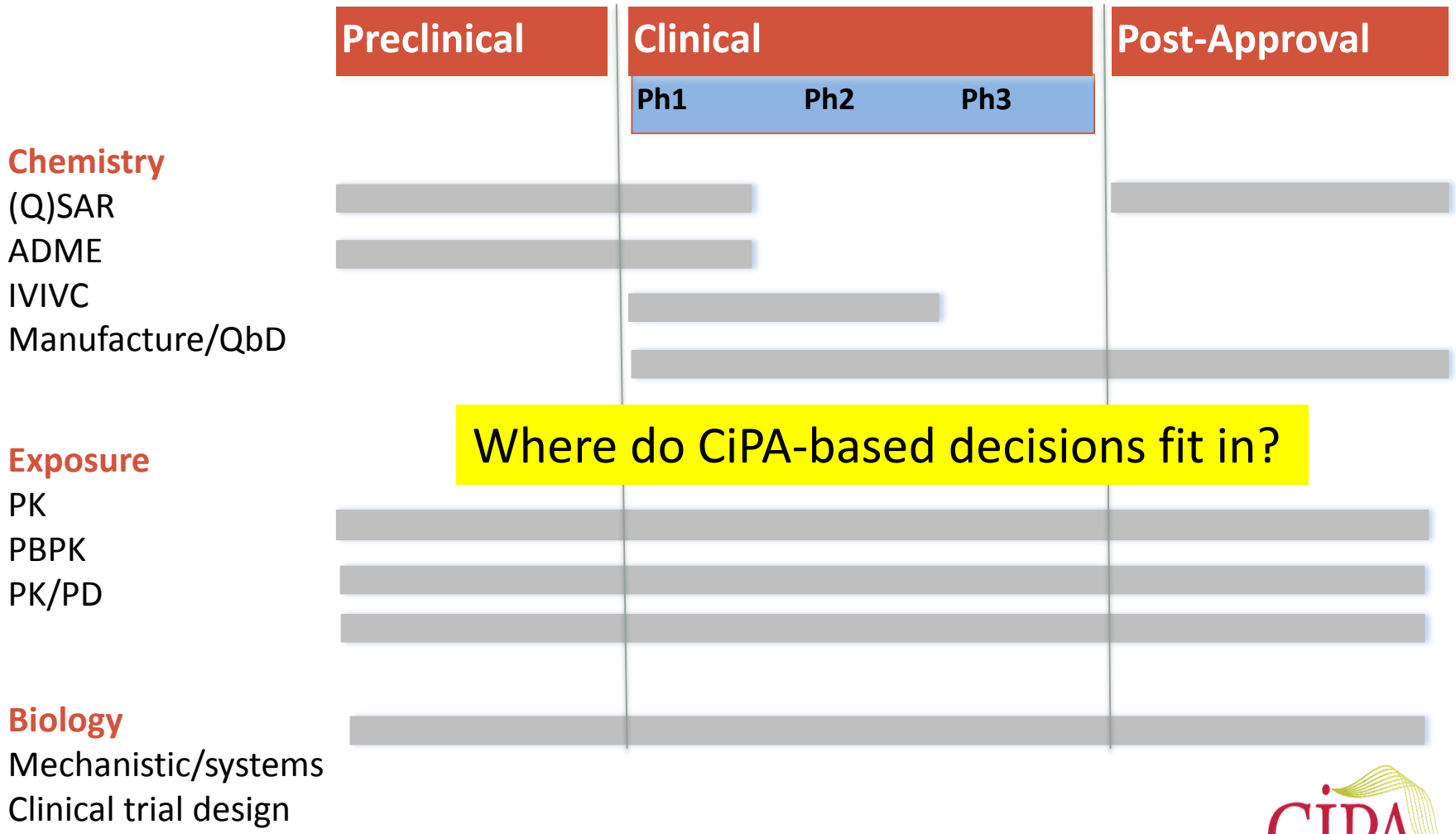
In Silico Models in Regulatory Review



Guidances Featuring Computer Modeling

(Q)SAR

- **Genotoxic and Carcinogenic Impurities In Drug Substances and Products: Recommended Approaches (2008)**
- **ANDAs: Impurities In Drug Substances (2009)**
- **ANDAs: Impurities Guidance Drug Products (2010)**
- **ICH M7: Carcinogenicity of DNA Reactive Impurities (2013)**

Pharmacokinetics

- **Population Pharmacokinetics (1999)**

PBPK

- **Drug Interactions Studies: Study Design, Data Analysis and Implications for Dosing and Labeling (2012)**

PKPD/Pharmacometrics

- **Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications (2003)**
- **End of Phase 2A Meetings (2009)**

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Regulatory Use of (Q)SAR Models

ICH M7: Carcinogenicity of DNA Reactive Impurities

- **Outlines the use of (Q)SAR models combined with expert analysis to evaluate the safety of drugs, metabolites, contaminants, excipients, degradants, etc.:**
  - when a regulatory decision must be made in the absence of adequate safety information on a chemical
  - when the submitted results of a safety study may be considered equivocal
- **These (Q)SAR models are:**
  - generally (commercially) available
  - informed and validated using large anonymized FDA data sets

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OECD Principles: (Q)SAR models

- **To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:**
  - A defined endpoint
  - An unambiguous algorithm
  - A defined domain of applicability
  - Appropriate measures of goodness-of-fit, robustness and predictivity
  - A mechanistic interpretation, if possible

Source: OECD Principle for the Validation, for Regulatory Purpose, of (Quantitative) Structure-Activity Relationship Models

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How the CiPA *In Silico* Approach Compares

Q(SAR) models

- **Binary decision (risk/no risk)**
- **Statistical**
- **Uses hundreds of compounds to develop and validate**
- **Informed by extensive sets of quantitative data**
- **Uses commercially available software**
- **Sponsors can run the same models used by FDA**

CiPA *in silico* model

- **Predicts degree of risk**
- **Mechanistic**
- **Uses only few compounds to develop and validate**
- **Calibrated using qualitative assessments of clinical risk**
- **Uses publicly available software (published)**
- **Sponsors can run the same models used by FDA**

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How Will This All Work?

- **Sponsors will provide "raw" patch clamp data to FDA for analysis and parameter extraction using the agency's HPC system and published algorithms**
- **A web-based portal will allow access to the *in silico* model, data sets and documentation for use in exploratory simulations and the secure entry of sponsor data**
- **If new data indicate the predictive performance of the model can be improved, it will likely be necessary to update the model and review how any changes impact prior predictions of relative risk**
- **As TdP risk may be assessed during drug discovery prior to knowledge about effective clinical drug levels, a range of concentrations will be evaluated to unmask behaviors mechanistically associated with TdP**

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Credibility of the CiPA *In Silico* Model

- **The O'Hara Rudy model was developed using "essential" experimental data from human heart and calibrated using human myocyte electrophysiology**
  - Experimentally verifiable
- **Drug-channel interactions are being modeled realistically**
- **The need to translate between assay data obtained on expressed channels and effects on native channels has been recognized and is being addressed**
- **The metric to be used must make sense mechanistically**
- **Calibration and validation of the model will be as intensive and exhaustive as the data allow**
  - This includes considering sources of variability and their effects on risk prediction

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Remember...

- Models will always be approximations of the “real world”
- Models can only be considered relevant and validated:
  - within a specific context of use
  - under clearly defined boundary conditions

“Models are to be used, not believed.”

- Henri Theil (econometrician)

“All models are wrong, but some are useful”

- George Box (statistician)

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