Principles of Proarrhythmia Models

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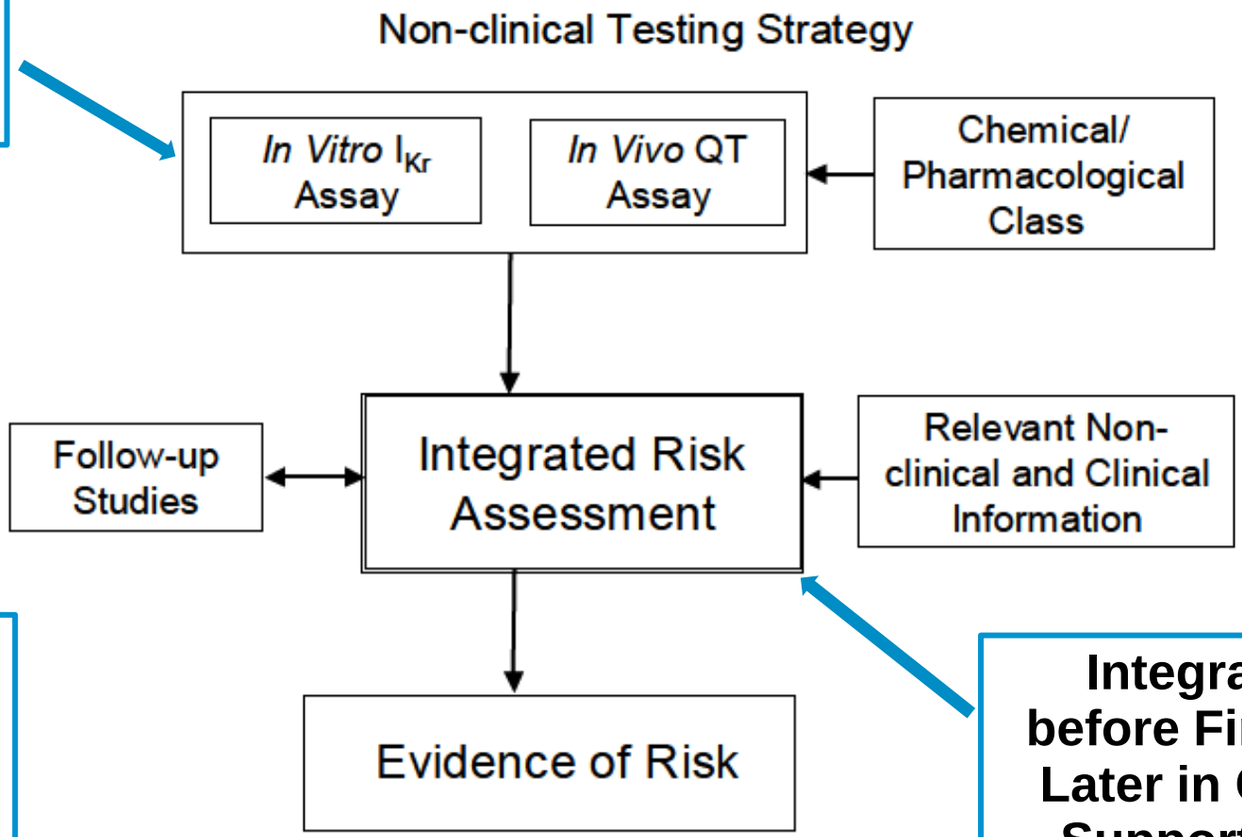
Background

"Best Practice" hERG/IKr & *in vivo* QT Assays



"Best Practice" Myocyte Assays & Principles of Proarrhythmia Models

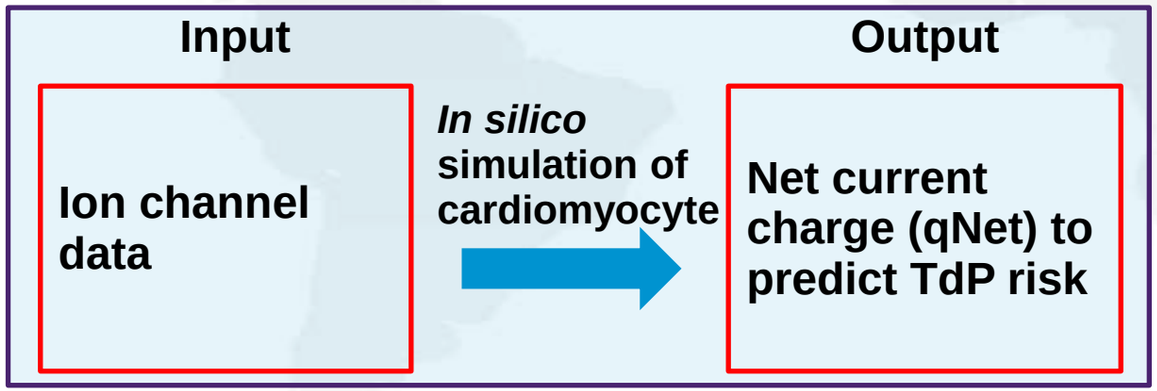
Integrated Risk Assessment before First-in-Human Dosing vs. Later in Clinical Development to Support Clinical Interpretation

Definition of Proarrhythmia Model

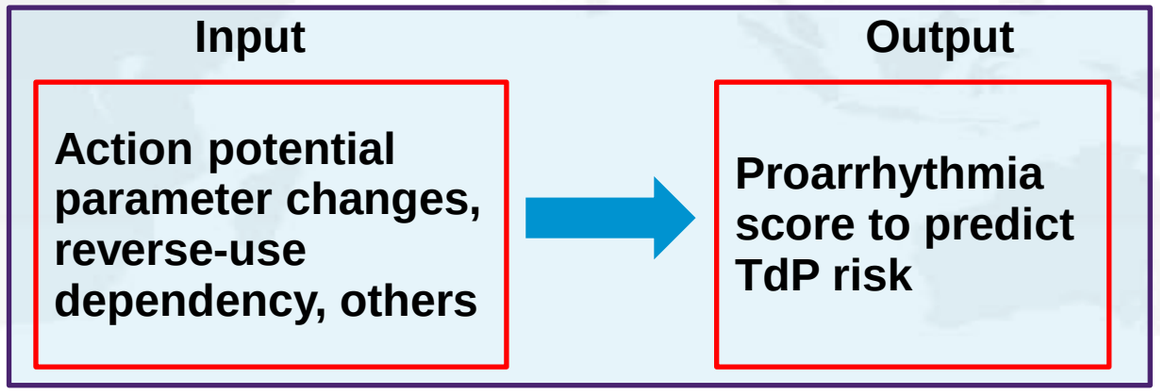
- **Proarrhythmia Model**
  - Including *in silico, in vitro, ex vivo, in vivo* models which can predict proarrhythmic potential
  - Should follow 6 principles to evaluate whether the model could be used as part of integrated risk assessment (to be discussed in the following slides)
- **Model input and output**
  - Model input: preclinical data for model prediction
    - *In silico* – ion channel data
    - *In vitro* – ion channel data, drug-induced repolarization change/arrhythmia
    - *Ex vivo/in vivo* – drug induced ECG parameter change/arrhythmia
  - Model output: Proarrhythmia metrics

Examples of Model Input and Output

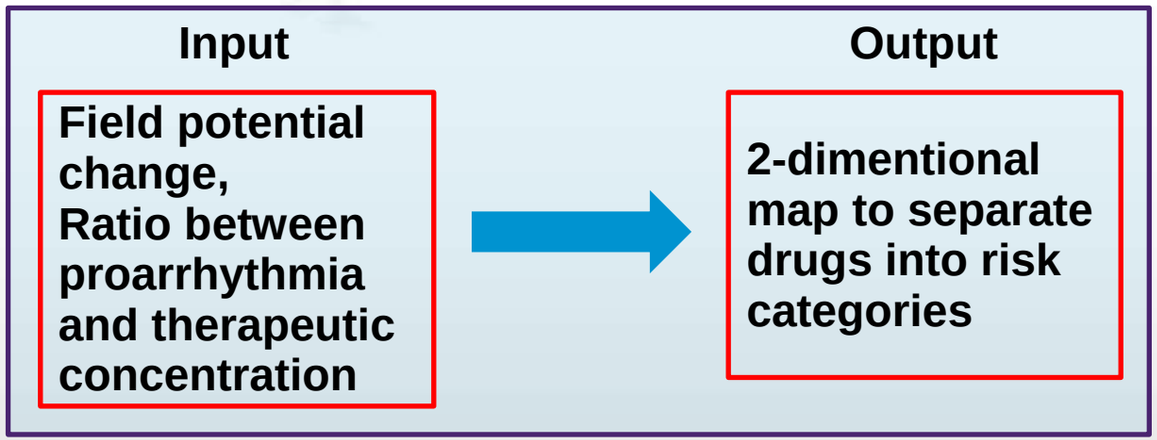
Ex.1: *In silico* (Li *et al*., 2018)



Ex.2: Canine Purkinje fiber (Champeroux *et al*., 2005)



Ex.3: iPSC-cardiomyocyte (Ando *et al*., 2017)



- **Proarrhythmia prediction model should follow 6 principles (next slide).**

Consistency and Integrity of General Principles

- In 2004, a set of principles for the validation of (quantitative) structure-activity relationship (QSAR) models for regulatory purpose was established by the Organization for Economic Co-operation and Development (OECD)
- These principles were adopted by ICH guideline M7 (R1) to evaluate the acceptability of QSAR models for the regulatory assessment of mutagenic impurities in pharmaceuticals
- The principles should also apply to proarrhythmia prediction models that are used as part of an integrated risk assessment for regulatory purposes (ICH S7B Q&A)

	OECD guideline for QSAR Model (2004)	White Paper (Li *et al*., 2019)	ICH S7B Q&A
Principle 1	defined endpoint	defined end point	defined endpoint
Principle 2	defined domain of applicability	defined domain of applicability	defined scope and limitations of model
Principle 3	appropriate measures of goodness-of–fit, robustness and predictivity	stringent strategy and predefined criteria	prespecified analysis plan and criteria
Principle 4	unambiguous algorithm	unambiguous algorithm	fully disclosed algorithm
Principle 5	mechanistic interpretation, if possible	mechanistic interpretation	uncertainty in the model input
Principle 6		uncertainty quantification	mechanistic interpretation

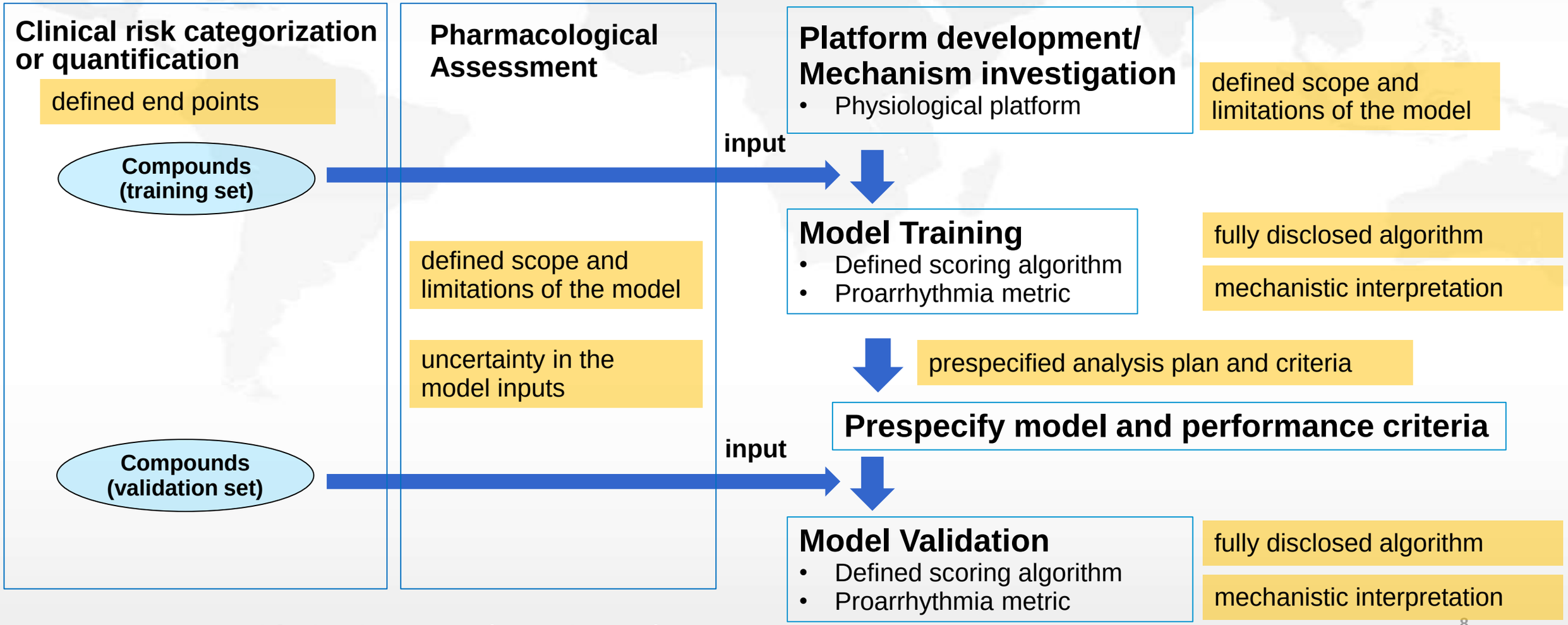
Principles in S7B Q&A

- **A defined endpoint consistent with the context of use of the model**
  - For TdP risk prediction, a series of reference drugs with known clinical TdP risk should be used to define the endpoint
- **A defined scope and limitations of the model**
  - Defined/standardized experimental protocol
  - Understand what mechanisms are covered (and not covered) by the model
- **A prespecified analysis plan and criteria to assess model predictivity**
  - Training and validation steps should be separated
  - Before validation, performance metric and acceptable criteria should be specified

Principles in S7B Q&A (Continued)

- **A fully disclosed algorithm to translate experimental measurements (model input) to proarrhythmia risk (model output)**
  - Enough transparency for independent evaluation of the model
- **Uncertainty quantification**
  - The uncertainty in the model inputs (experimental measurements) should be captured and propagated to the model predictions
- **A mechanistic interpretation**
  - Need to describe the relationship between model inputs (experimental measurements) and mechanism of arrhythmia

Model Development Process

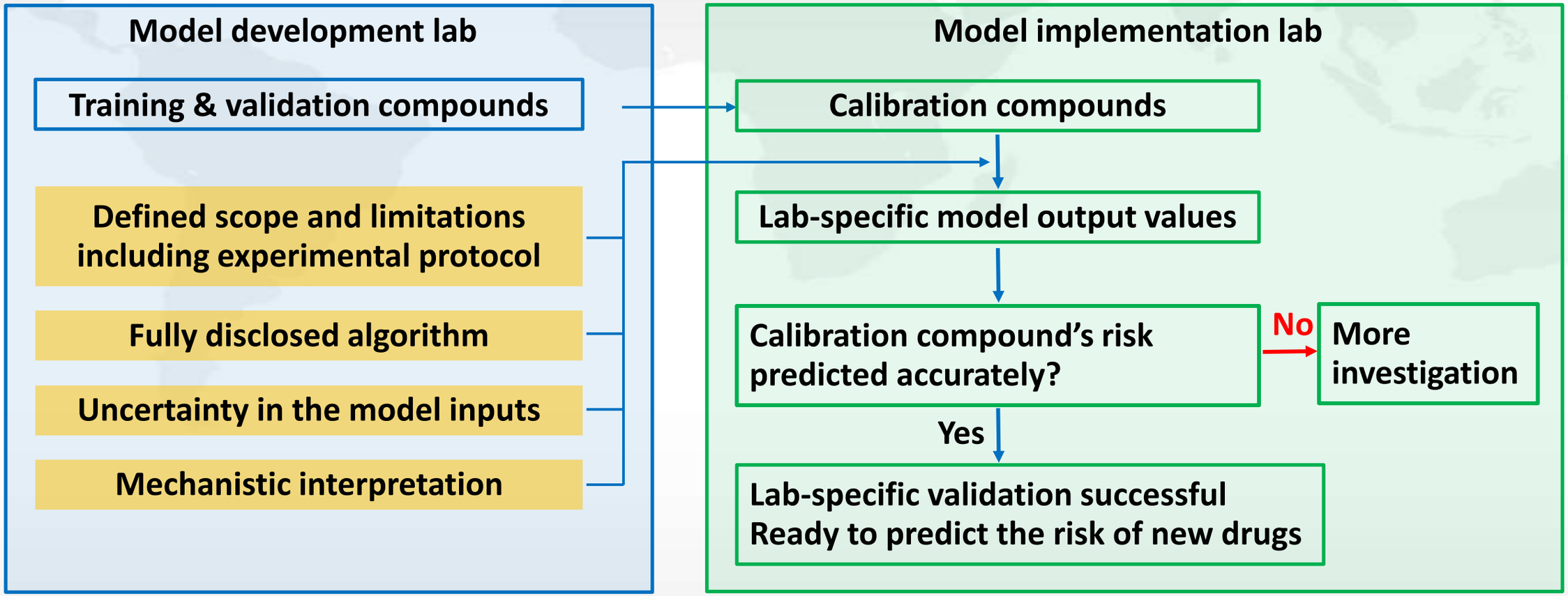


Modified, White Paper (Li *et al.*, 2019)

Model Implementation

- **After a model was developed by a laboratory (lab) using a series of reference compounds, the model can be used by other labs (model implementation)**
- **New labs should use a subset of the reference compounds to internally calibrate and validate the model**
- **Examples of selecting the subset calibration compounds, and performing lab-specific calibration and validation: Han *et al*., 2020.**

Model Implementation Process



Modified, Han *et al.*, 2020

Hypothetical Example: When a Sponsor Uses the Model

- A sponsor submits an application for drug A
- It is not double negative (i.e. it has a positive hERG and/or *in vivo* QT signal).
- Follow-up studies demonstrated that drug A blocks IKr/hERG and an inward current (e.g. L-type calcium current, late sodium current)
- In the application, the sponsor referenced an ion channel/*in silico* model previously published (or previously went through a qualification process with the regulator) and showed that the model development follows all the 6 principles
- The sponsor (or contract research organization), although not the original model developer, used a subset of reference compounds to internally calibrate and validate the model
- The sponsor then tested the new drug and the model predicts drug A has “low TdP risk”. This “low TdP risk” prediction will be used together with other information to inform subsequent clinical investigation and decision making.

Points to Consider for Regulatory Submission

- **Use of the model only under the context of use for which it was developed**
- **Set of control compounds should be tested to assess the consistency between the new data and the historical lab-specific validation data, i.e. to demonstrate reproducibility of the assay/model**
- **Some regulatory authorities require formal qualification of models**
- **When the model is included in a regulatory submission, supporting documentation should be provided**

Summary

- **A proarrhythmia risk assessment model could be used as follow-up investigation when nonclinical core assays are not negative (part of the integrated risk assessment)**
- **The model should have been qualified under consideration of the general principles presented in the Q&A**
- **The models can be used not only by developer but also by other labs with lab-specific validation data**

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Thank you!

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