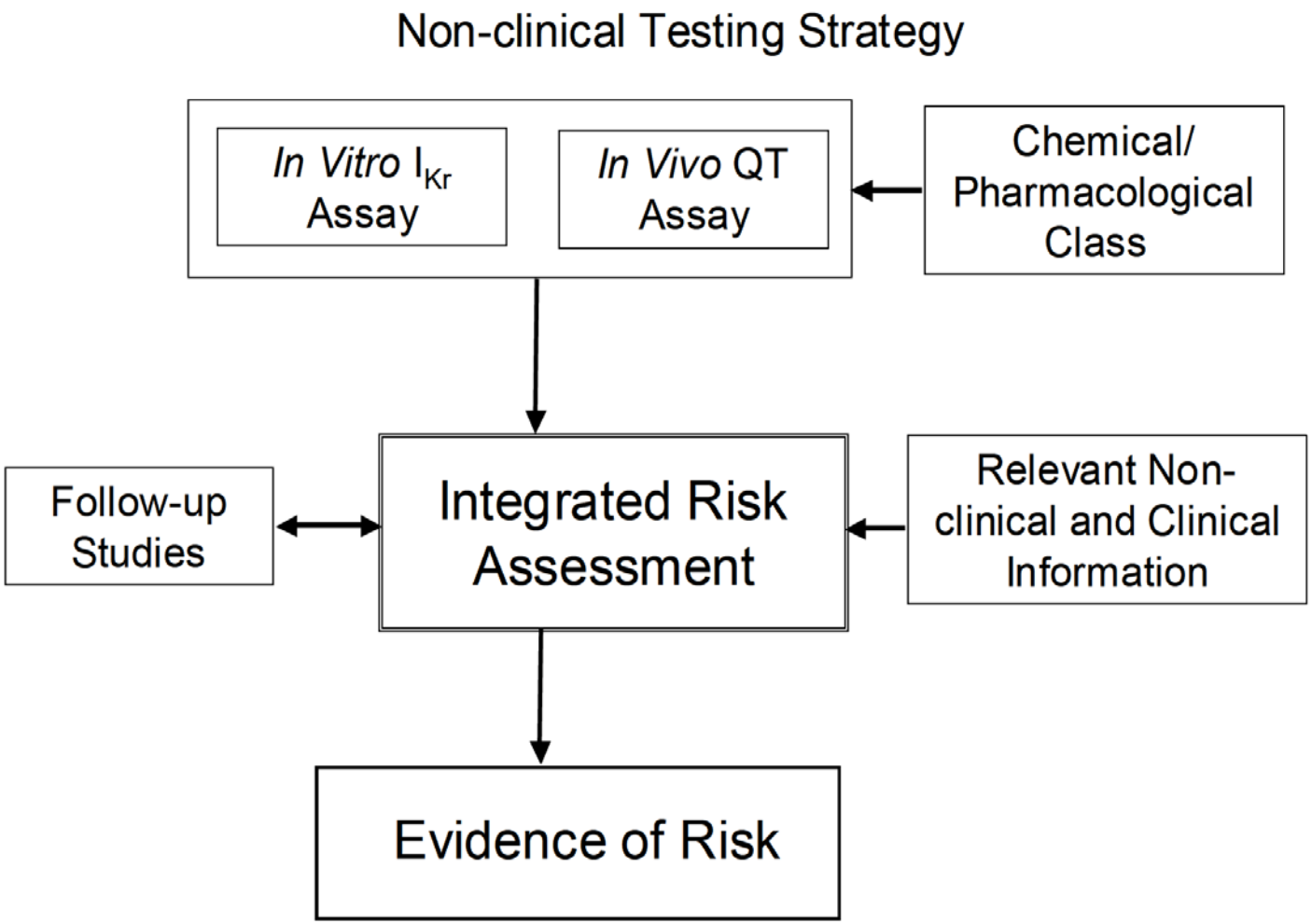
What aspects of the non-clinical data increase confidence in this data in an integrated approach of QT data?

John Koerner, Ph.D.
FDA/CDER/DCRP

Disclaimer

- The thoughts expressed here are those of the speaker and do not necessarily reflect those of the FDA.

ICH S7B (2005)


Non-clinical Testing Strategy
In Vitro I_{Kr} Assay
In Vivo QT Assay
Chemical/ Pharmacological Class
Follow-up Studies
Integrated Risk Assessment
Relevant Non-clinical and Clinical Information
Evidence of Risk

HESI/FDA Nonclinical QT to TQT Concordance Project

- Question: How well does nonclinical QT data predict TQT study results?
- Quantitative evaluation, i.e., concentration response
- Data provided to the agency in support of INDs and NDAs

Preliminary Evaluation Gaps, all assays

Limited to big gaps

Appropriate Doses/Concentrations Not Tested

- Doses and concentrations tested were below therapeutic levels in many cases
- *Recommendation: Test appropriate concentrations, including therapeutic and supratherapeutic concentrations*

In Vivo ECG Assay

Experimental Design

- Huge variation in experimental design and analysis
  - Latin square crossover vs parallel designs
  - Sample size
  - Dosing regime
  - Dose(s) tested
  - Data analysis
- *Recommendation: Consider a standard design/analysis methodology*

Plasma Drug Levels

- In many cases, we needed to obtain plasma drug levels from a separate study.
  - At the test dose, sometimes
  - At a different dose, sometimes
- *Recommendation: Measure plasma drug levels concurrently in the in vivo QT study*

Assay Sensitivity

- What effect size can be ruled out?
  - Statistical power
  - Historical control data
  - Concurrent positive control
- *Recommendations*
  - *Provide information on assay sensitivity, and the effect size that can be ruled out.*
  - *Power the study to capture a clinically relevant effect.*
  - *Include concurrent positive control.*

In Vitro Assay

Assay Sensitivity

- Assessed by inclusion of a concurrent positive control drug
  - Concentrations tested too high
    - Supratherapeutic concentration does not address assay sensitivity
- *Recommendation: Test concurrent positive control at appropriate concentration, i.e., IC50*

In vitro to in vivo extrapolation

- IC50/free plasma drug ratio
- Free plasma drug levels may not reflect tissue levels, particularly for highly plasma protein bound drugs.
- *Recommendation: Consider measuring cardiac tissue drug levels in animals*

Consider additional assays

Trafficking (hERG)

- Trafficking inhibition accounts for QT prolongation with some drugs, e.g., arsenic trioxide
- hERG voltage clamp and in vivo assays are unlikely to capture such drugs
- *Recommendation: Incorporate trafficking inhibition assay into core battery*

Additional Ionic Currents

- Hypothesis: Evaluation of drug effects on sodium, calcium and hERG currents is more predictive than evaluating drug effects on hERG alone
- *Recommendation: Test this hypothesis*

Single Cell Repolarization Assays

- Multicellular preparations can miss effects of multichannel blockers, e.g., terfenadine.
- Hypothesis: Single cell preparations can capture such drugs
  - Isolated ventricular myocytes
  - Stem cell-derived cardiomyocytes
- *Recommendation: Test this hypothesis*

PK/PD in Animals

- PK/PD can be a powerful tool in the clinical evaluation of QT prolongation
- Hypothesis: Animal PK/PD predicts human PK/PD.
- *Recommendation: Test this hypothesis*

Summary Recommendations

- Test appropriate doses/concentrations
- Measure plasma drug levels concurrently
- Address assay sensitivity
  - Positive control (concurrent)
    - dose that produces a small effect size

Additional Assays

- Trafficking –YES

- Additional ionic currents
- Single cell repolarization assays
- PK/PD in animals

Thank you