# S7B Integrated Risk Assessment

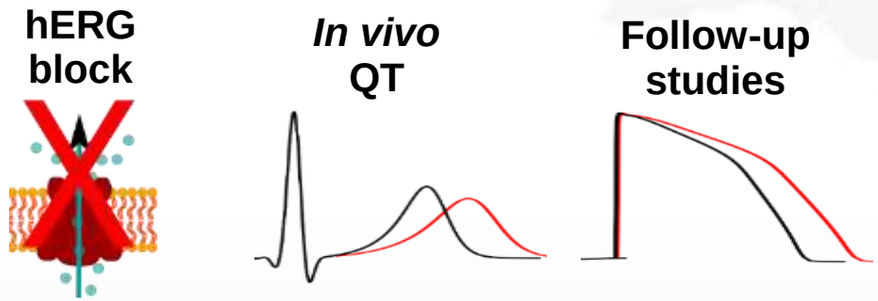
**Zhihua Li, PhD**
**Expert, ICH E14/S7B Implementation Working Group**
**FDA, United States**

International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

# ICH S7B: History and Impact

- **Established in 2005 after multiple drugs removed from market due to Torsade de Pointes (TdP)**

- **S7B: Nonclinical cardiac safety pharmacology**
  - hERG potassium channel block
  - Nonclinical *in vivo* QT study
  - Follow-up studies as needed



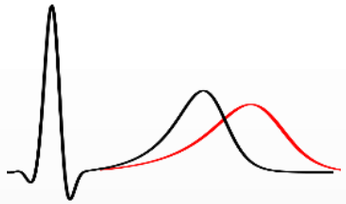

- **Successful in keeping study participants safe in early clinical trials**

# ICH S7B: Room for Improvement

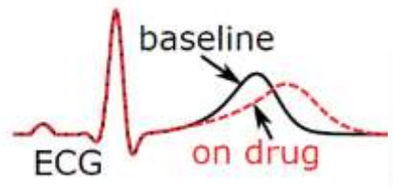
- **Limited guidance on some experimental details has led to variability in assay performance and …**

- **As clinical development continues, nonclinical studies are largely ignored and clinical safety assessment relies on human QT, which is an imperfect biomarker**

**Nonclinical**



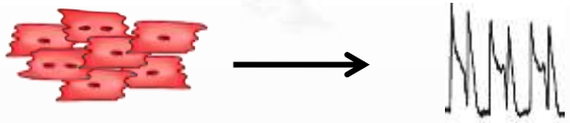
**Clinical**



# S7B Testing Strategy and Stage 1 Q&A Focus

**"Best practice" considerations* for ion channel assays** (Q&A 2.1) and ***in vivo* QT assays** (Q&As 3.1-3.5)

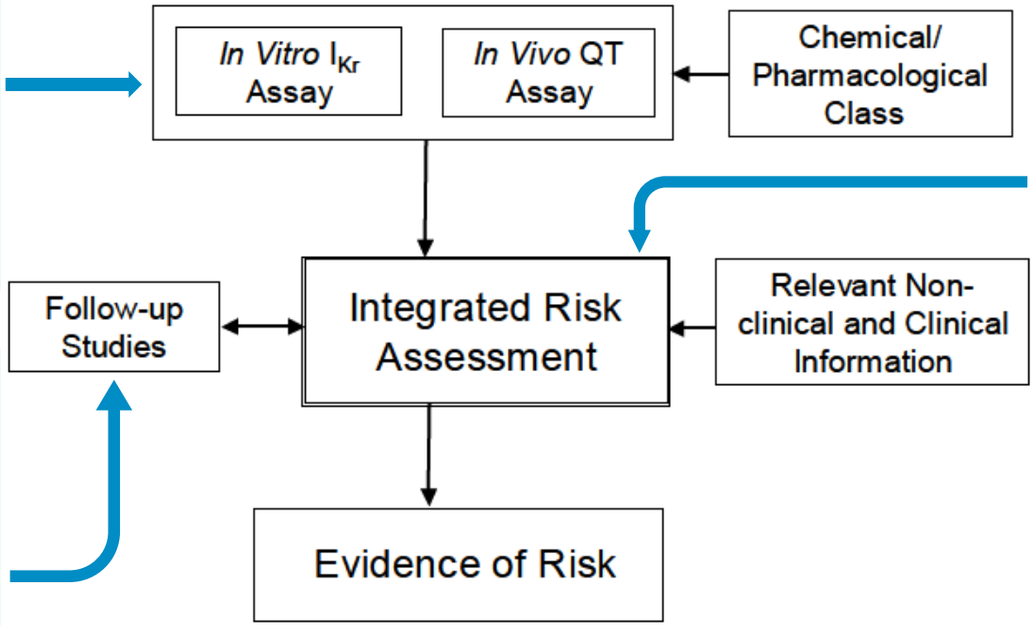

**"Best practice" considerations for myocyte assays** (Q&As 2.2-2.5)



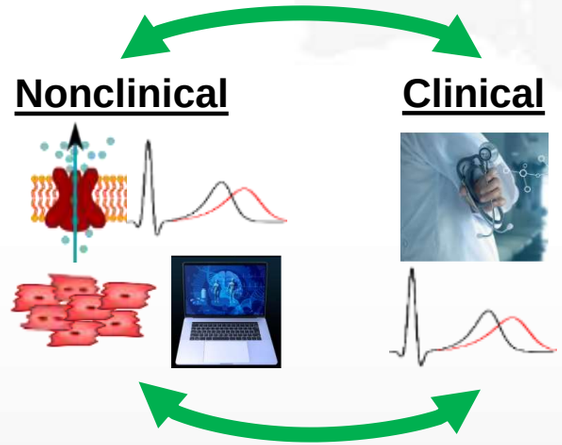
**Principles for proarrhythmia models** (Q&As 4.1-4.2)


**Current S7B Guideline**

Non-clinical Testing Strategy




**Integrated risk assessment considerations** when nonclinical data is used prior to human testing vs. later in clinical development for E14 scenarios (Q&As 1.1-1.2)




**Best practice considerations are not intended to impact a sponsor's screening activities. Some considerations only apply when using nonclinical data for clinical scenarios under E14 Q&As 5.1 and 6.1.*

# ICH S7B Integrated Risk Assessment Questions

- **Question 1.1: What is the general strategy for use of nonclinical information as part of an integrated risk assessment for delayed ventricular repolarization and torsade de pointes that can inform the design of clinical investigations and interpretation of their results?**

- **Question 1.2: What is the recommended method to compute the hERG safety margin?**

# Overview of the Nonclinical Integrated Risk Assessment

- **Two scenarios to use nonclinical data to inform clinical decision-making**
  - Double negative scenario
    - When the *in vitro* hERG assay and *in vivo* QT assay are negative
  - Non-double negative scenario
    - When the *in vitro* hERG assay and/or *in vivo* QT assay are positive
- **Principles to define "negative hERG assay" and "negative *in vivo* QT assay" are provided in the Q&A**
  - Current ICH S7B guideline does not specify how to define a negative core assay

# Principles to Define a Negative hERG Assay

- **hERG safety margin (hERG IC50 / Cmax) of a new drug is higher than the safety margin determined based on reference drugs known to cause TdP**
  - Experimental variability should be incorporated in hERG safety margin calculations (IC50 variabilities translated to confidence interval around the safety margin)
- **hERG IC50 should be determined following Q&A 2.1 "best practice" considerations**
  - The same experimental protocol should be applied to the new drug and the reference drugs
- **Cmax = Mean steady state maximum plasma concentration when the maximum recommended therapeutic dose is given with intrinsic or extrinsic factors (high clinical exposure scenario)**
  - High clinical exposure will be an estimate early in development that is subsequently refined
  - Free (unbound) fraction of plasma concentration is usually used
    - Free fraction should be set to 1% if experimentally determined to be < 1%*
    - If protein binding cannot be accurately assessed, or tissue levels may exceed free plasma concentrations, both free and total Cmax should be used

***consistent with FDA Guidance document on drug interaction studies: https://www.fda.gov/media/134582/download**

# Principles to Define a Negative *In Vivo* QT Assay

- **No QT prolongation in animal studies when a new drug's exposure includes and exceeds anticipated clinical exposure**
- **Both the parent and any major human metabolites need to be considered**
- **Experiments should follow general *in vivo* best practice considerations**
  - e.g., species selection, heart rate correction, reporting format
- **To support E14 Q&As 5.1 and 6.1, exposures should cover the anticipated high clinical exposure scenario. The adequacy of exposure to any major human-specific metabolites should be determined (see ICH S7A and S7B).**
- **To support E14 Q&A 6.1, the *in vivo* study should have the power to detect a QTc prolongation of a magnitude similar to dedicated clinical QT studies**

# Double Negative Scenarios to Inform Clinical Decision Making

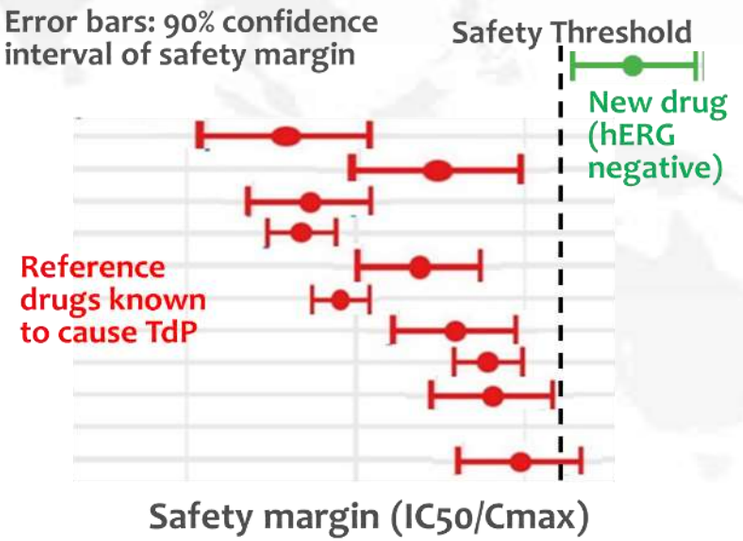
- **Lower clinical exposure needed to waive the positive control (E14 Q&A 5.1)**
  - *In vivo* QT study should cover the anticipated high clinical exposure
- **Alternative clinical QT study design (E14 Q&A 6.1)**
  - *In vivo* QT study doses should cover the anticipated high clinical exposure
  - *In vivo* QT assay should be powered to detect QTc prolongation of a magnitude similar to a dedicated clinical QT studies

# Example 1: Double Negative Scenario to Support E14 Q&A 5.1

- **Clinical Data:**
  - First-in-human study with high-quality ECGs
  - Highest dose covers the exposure expected when the drug is given with concomitant strong CYP inhibitor (i.e., high clinical exposure scenario)
  - Concentration-QTc analysis rules out 10 msec effect at high clinical exposure
  - No QTc positive control
- **Question: Can the First-in-human study serve as a substitute for a TQT study?**
  - Under the current E14 Q&A (R3) 5.1: **No**
  - Under the new E14/S7B Q&A: **see next slide**

# Example 1: Double Negative Scenario to Support E14 Q&A 5.1

- **Nonclinical Data**:
  - *In vitro* IKr/hERG assay
    - Assays conducted following the best practice (S7B Q&A 2.1) and other considerations (S7B Q&As 1.1-1.2)
    - Safety threshold determined using reference drugs with known TdP risk, and a justification of choosing this threshold and reference drugs
    - With the same experimental protocol, new drug's safety margin > this threshold
  - *In vivo* QT assay
    - Assays conducted following best practice considerations (S7B Q&As 3.1 – 3.5)
    - No QTc prolongation at concentrations of parent compound and human-specific metabolites that cover high clinical exposure




- **Regulatory outcome: Integrated clinical and nonclinical risk assessment can substitute for a TQT study**
  - Only possible with the new Q&A

# Example 2: Double Negative Scenario to Support E14 Q&A 6.1

- **Clinical data:**
  - Uncontrolled, dose-escalation study with expansion cohort for an oncology drug
  - Highest dose studied was the labeled dose
  - No evidence of QTc prolongation using concentration-response relationship and no important QTc outliers
  - Cardiac safety database at market application does not suggest proarrhythmic risk
- **Question: Can the clinical QT assessment support low risk for QTc prolongation or TdP?**
  - Under the current E14 Q&A (R3) 6.1: No
  - Under the new Q&A: see next slide

# Example 2: Double Negative Scenario to Support E14 Q&A 6.1

- **Nonclinical data:**
  - Negative *in vitro* hERG assay: same as the E14 Q&A 5.1 example
  - Negative *in vivo* QT assay: same as the E14 Q&A 5.1 example, plus demonstration that the *in vivo* QT assay was powered to detect QT prolongation of a magnitude similar to a dedicated human QT study
- **Regulatory outcome: Integrated clinical and nonclinical risk assessment supports the clinical interpretation of low TdP risk**
  - Only possible with the new Q&A

# Non-Double Negative Scenario

- **Follow-up studies may be performed to further evaluate TdP risk on a case-by-case scenario**
- **Best practice considerations for some follow-up studies are described in S7B Q&As:**
  - Additional ion channels (Q&A 2.1)
  - Human derived cardiomyocytes (Q&As 2.2 - 2.4)
  - Proarrhythmia risk prediction models (can be *in vitro*, *in silico*, *in vivo*, *ex vivo*) to quantify TdP risk level (Q&As 4.1 - 4.3)
- **Follow-up studies are optional**

# Example 3: The Use of Follow-up Studies

- **Clinical data:**
  - First-in-human (both single and multiple ascending dose) studies with high-quality ECGs
  - Highest dose evaluated covers the high clinical exposure scenario
  - Exposure-response data rule out 10 msec QTc prolongation and suggest no relationship between concentration and QTc (and no relationship with PR or QRS intervals)
  - No positive control for QTc
- **Nonclinical core assay data could not be used to waive positive control**
  - Negative *in vivo* QT assay: the same as the E14 Q&A 5.1 example
  - *In vitro* IKr/hERG assay conducted the same as the E14 Q&A 5.1 example, however:
    - Drug's safety margin is slightly lower than the safety threshold based on reference drugs

# Example 3: The Use of Follow-up Studies

- **Follow up studies suggested low TdP risk**
  - Additional ion channel studies suggested drug blocks both IKr/hERG and an inward current. For example, late sodium current (INaL), L-type calcium current (ICaL)
  - A qualified *in silico* model quantified the block effects and predicted a low TdP risk
  - A cardiomyocyte study did not demonstrate any proarrhythmia events
- **Regulatory outcome: only routine safety ECG monitoring is needed in later development**
  - subject to case-by-case evaluation

# Follow-up Studies for Drugs Prolonging QTc Interval

- **Second Stage: S7B and E14 Q&As on how to use proarrhythmia prediction models or algorithms:**
  - To influence the design of late phase trials (e.g., intensity of ECG monitoring, eligibility criteria, stopping rules) and to inform labeling for QT prolonging drugs

**Influence phase 3 clinical trial design**

For QT prolongers

**Inform labeling**

Low Risk

- **The integrated risk assessment, including the results from follow-up studies and other relevant clinical and nonclinical information, can contribute to the design of subsequent clinical investigations and interpretation of their results**
  - first stated in the S7B guideline and re-iterated in the draft S7B Q&A 1.1

# Summary

- **S7B should continue to be followed for obtaining nonclinical data to support first-in-human studies**
- **The new integrated risk assessment Q&As provide additional recommendations when nonclinical data are used later in clinical development**
  - Applying best practice (Q&As 2.1 and 3.1-3.5) is encouraged and might prevent repeat assays during clinical development
- **Double negative nonclinical assessments (*in vitro* hERG and *in vivo* QT) can be used to support E14 Q&As 5.1 & 6.1**
- **Optional follow-up studies can be used to further evaluate QT/TdP risk when nonclinical core assays are not negative**

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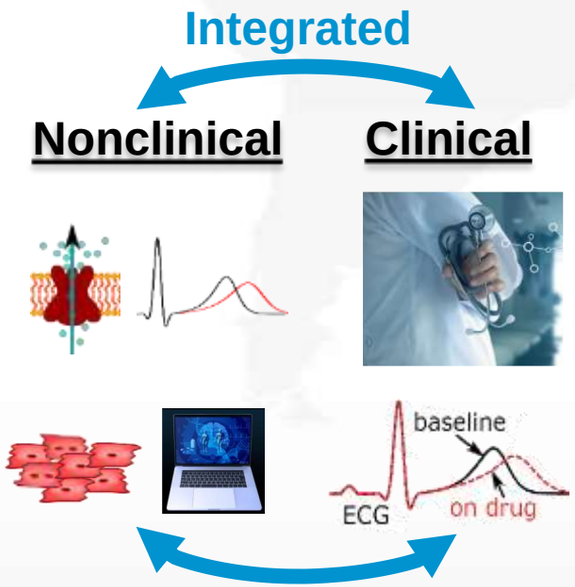
# Day 1 Schedule

**E14 Scenarios and Integrated Risk Assessment**




- ✓ **Background, Motivation for and Overview of the New Q&As for ICH E14 and S7B**
  - ✓ **David Strauss, *FDA, United States***
- ✓ **Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation**
  - ✓ **Christine Garnett, *FDA, United States***
- ✓ **S7B Integrated Risk Assessment Q&As**
  - ✓ **Zhihua Li, *FDA, United States***
- ➢ **Considerations for an Integrated Nonclinical-Clinical Risk Assessment**
  - **Jean-Pierre Valentin, *EFPIA***
- ➢ ***Discussion of Questions Received from the Q&A Pod***
  - **Facilitators: David Strauss, *FDA, United States* and Derek Leishman, *PhRMA***
  - **All Speakers and Flora Musuamba, *EC, Europe*; Colette Strnadova, *Health Canada, Canada*; Charles Benson, *EFPIA***