Background, Motivation for and Overview of the New Questions & Answers for ICH E14 and S7B

David Strauss, MD, PhD

Rapporteur, ICH E14/S7B Implementation Working Group
FDA, United States

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

Clinical Problem – Drug-Induced Torsade de Pointes

Normal

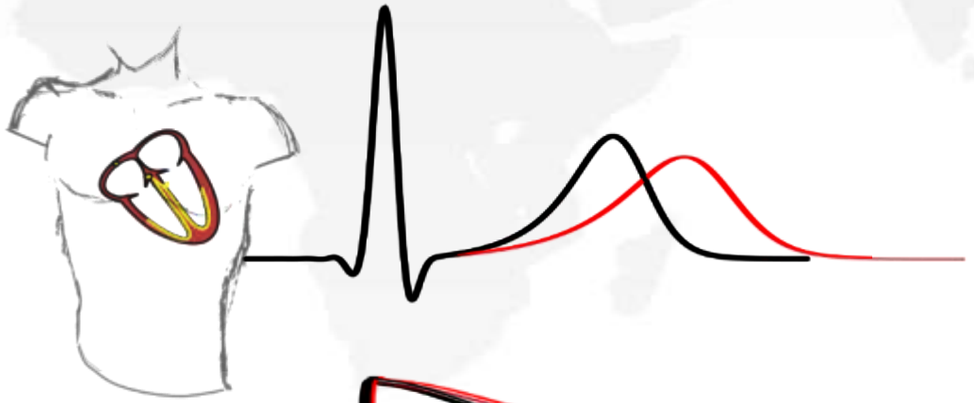
Torsade de Pointes (TdP)

"Twisting of the Points"

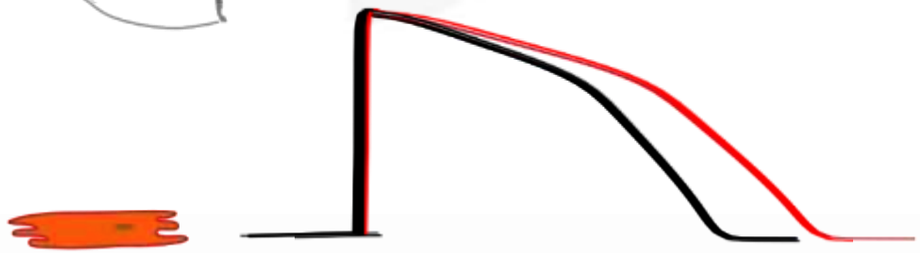
sometimes

What Do TdP Drugs Have in Common?

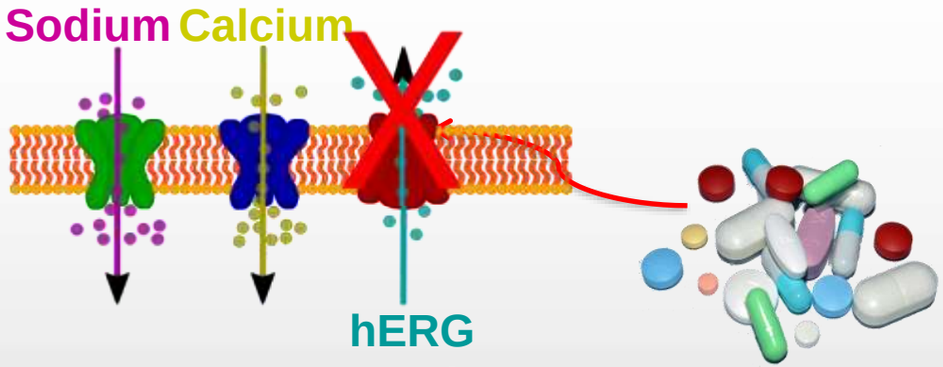
QT prolongation



Action potential prolongation



hERG (IKr) channel block



International Council for Harmonisation (ICH)

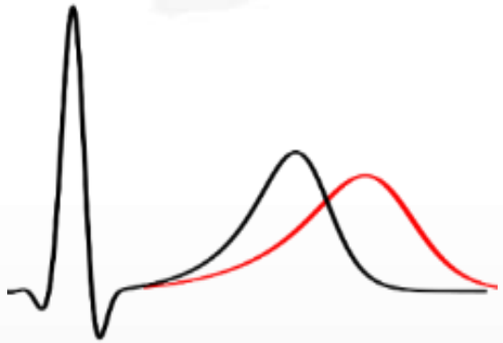
- **Founded in 1990 (currently 17 member organizations and 32 observer organizations)**
- **Mission: To achieve greater harmonisation worldwide to ensure safe, effective and high-quality medicines are developed and registered in the most resource-efficient manner**

International Council for Harmonisation (ICH) S7B Guideline: History and Impact

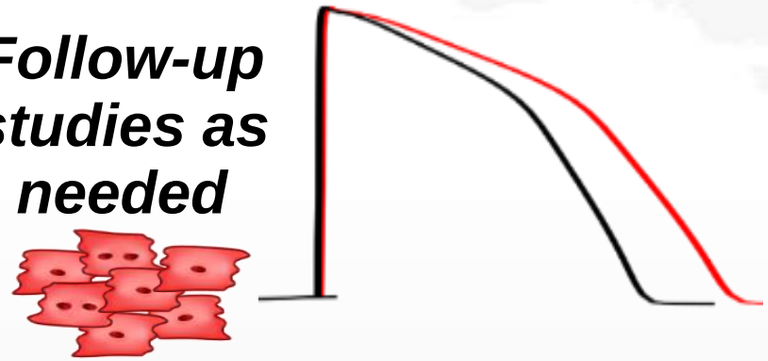
- **Established in 2005**
- **Nonclinical cardiac safety pharmacology guideline focused on assessing whether a drug:**

Blocks hERG

Prolongs QT



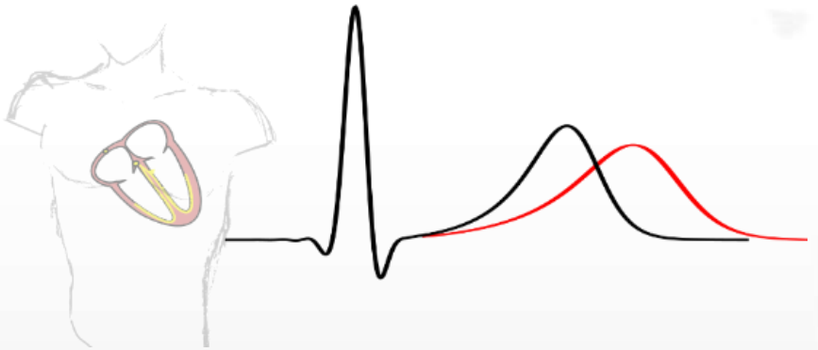
Follow-up studies as needed



- **Successful in bringing investigational drugs forward safely into first-in-human studies**

ICH E14 Guideline: History and Impact

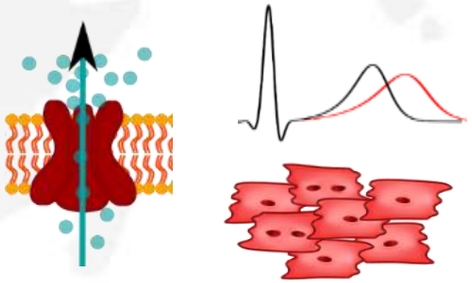
- **Established in 2005**
- **Clinical guideline describing the human 'Thorough QT' (TQT) study**
  - Established very sensitive threshold for ruling out TdP risk (~2% increase in QT – very small!)
  - Most intensive & expensive clinical pharmacology study
  - Multiple prior E14 Q&As
  - Successful in preventing drugs with unknown TdP risk from reaching the market



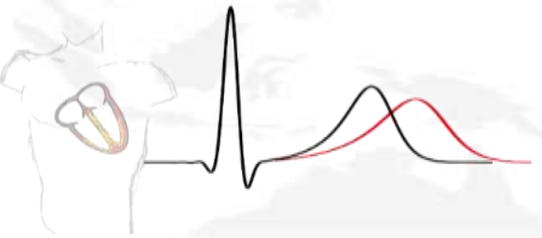
ICH E14 & S7B: Room for Improvement

- **S7B studies inform safety before first-in-human dosing but then are largely ignored**
- **Clinical assessment relies on human QT, which is an imperfect biomarker**

Nonclinical

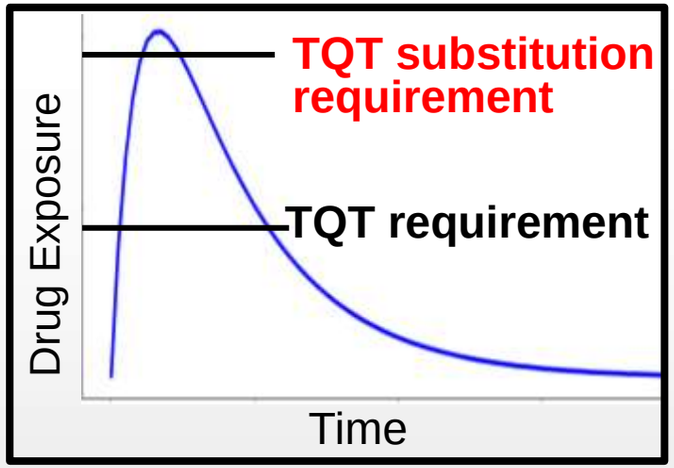


Clinical



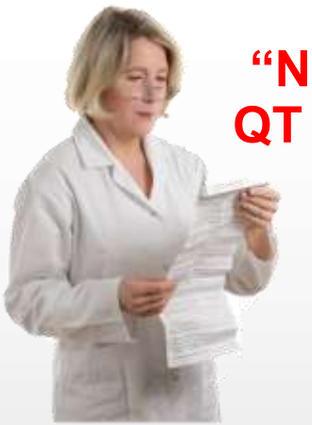
- **Prior E14 Q&As only allow for TQT study 'substitution'** (with phase 1 concentration-QTc) **under narrow requirements**

Very high exposure required!



- **Prior E14 Q&As only allow for limited decision-making when a TQT study** (or TQT 'substitute') **cannot be performed**

Unclear risk

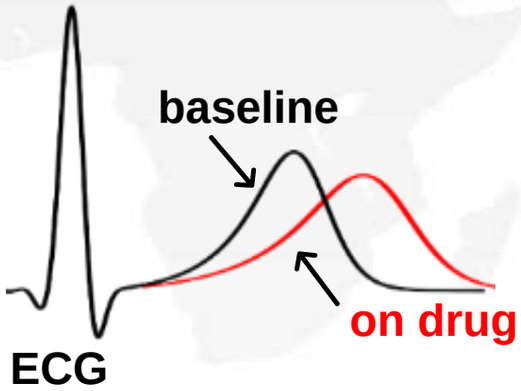


"No Large QT Effects" label

ICH E14 & S7B: Room for Improvement (continued)

E14 stated TQT goal

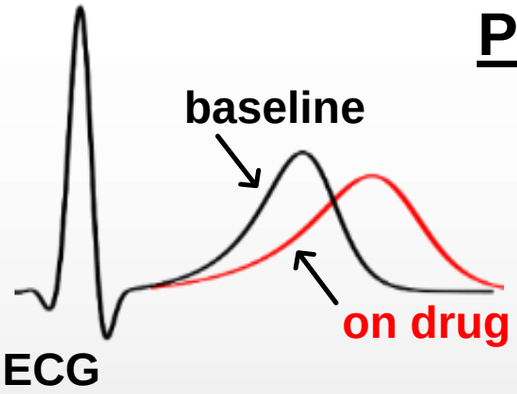
- **E14 states: TQT study is intended to inform whether ECG monitoring is required in phase 3 trials as not all QT prolonging drugs are proarrhythmic**



ECG monitoring in phase 3

Practice

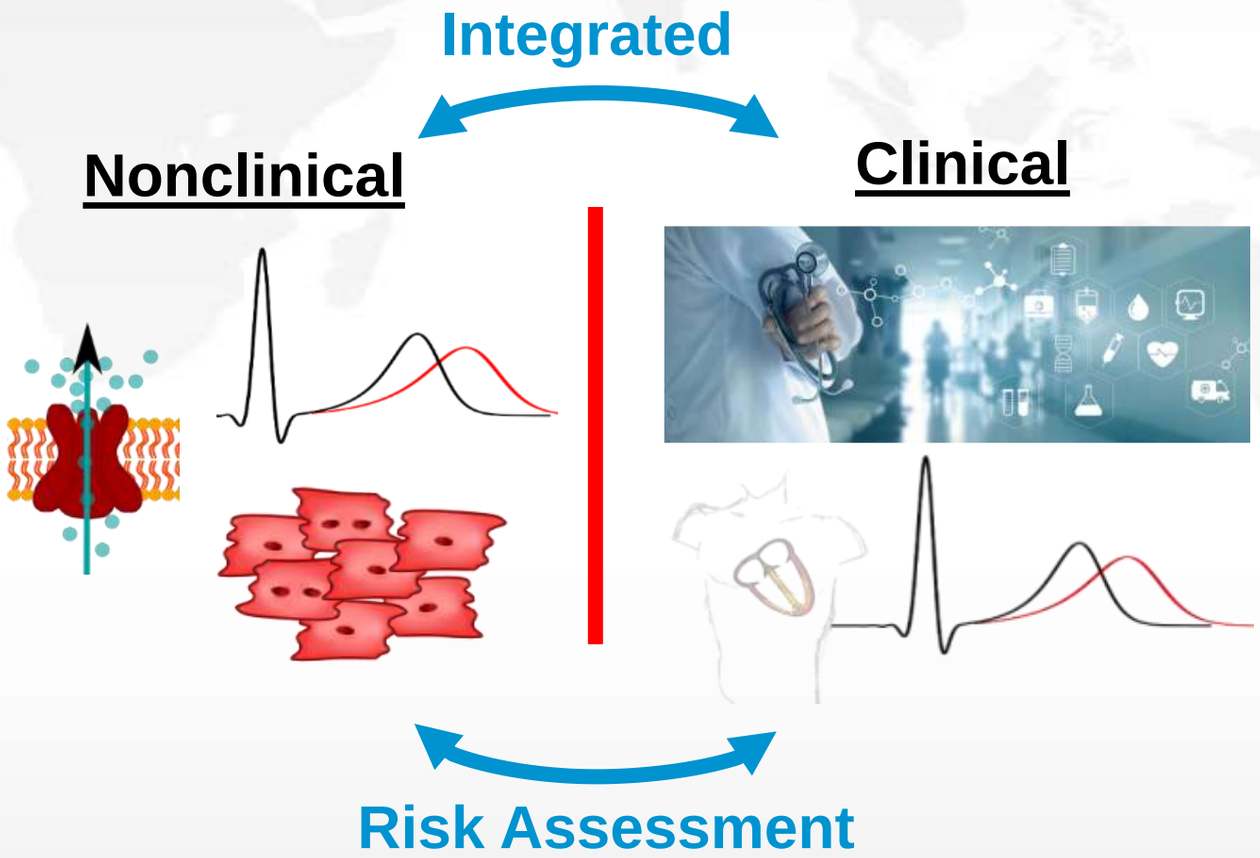
- **However: Drugs with a 'positive' hERG or QT signal are often dropped from development**



Dropped from development

Opportunity for New E14/S7B Q&As

- **While at adoption E14 suggested a QT interval evaluation independent of S7B results …**
- **Both documents highlight the need for integration of information in a manner which is informative as a totality of evidence**



Value Proposition of New E14/S7B Q&As

Directed at scenarios where nonclinical data can:

Reduce number of clinical studies

TQTs

TQTs

Inform clinical regulatory decision making at the time of a marketing application

NDA = new drug application

Streamline drug development

Inform labeling to better communicate risk

"No Large QT Effects" → Low Risk

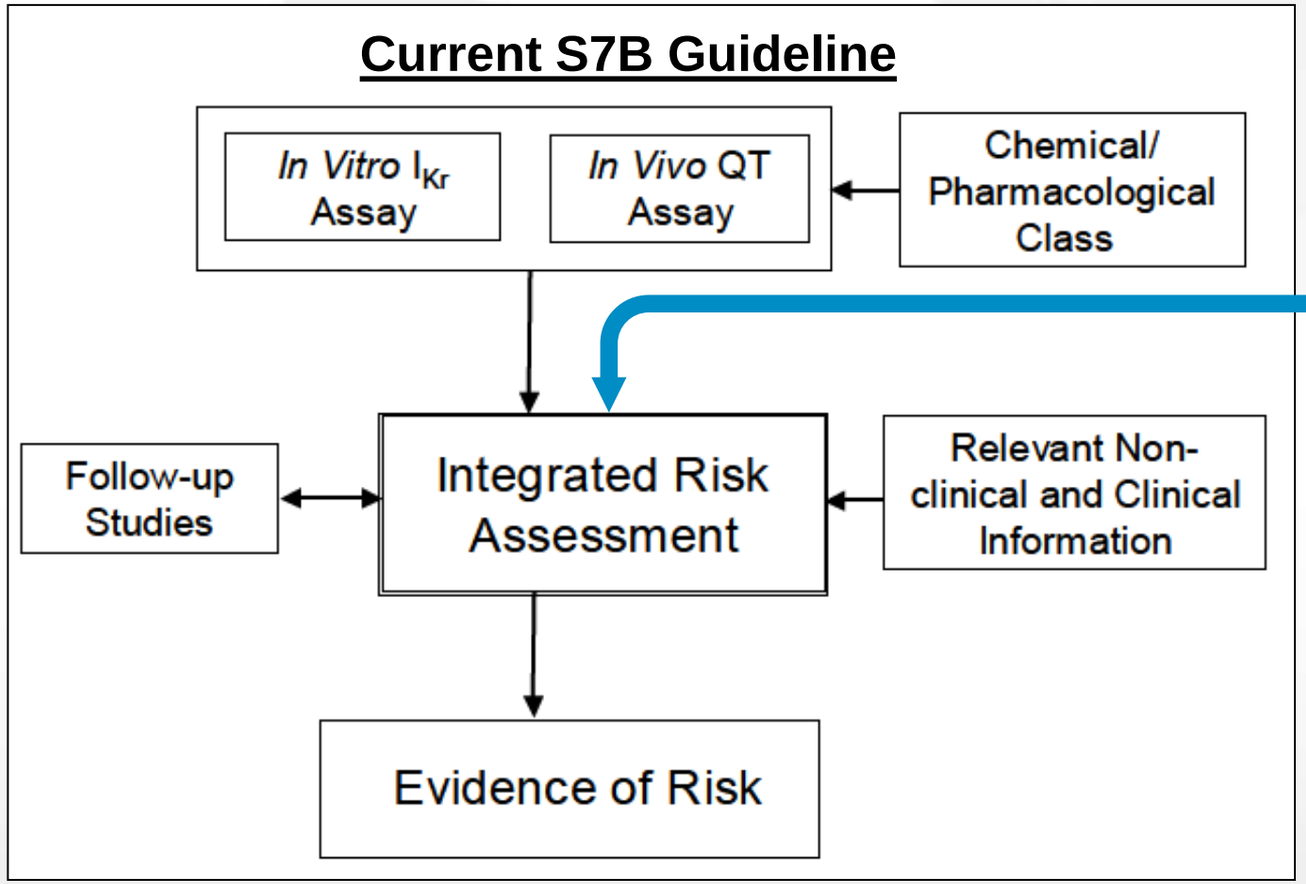
Strategy to Link S7B & E14

E14/S7B group reached agreement in 2018 on a two-stage approach

Stage 1:

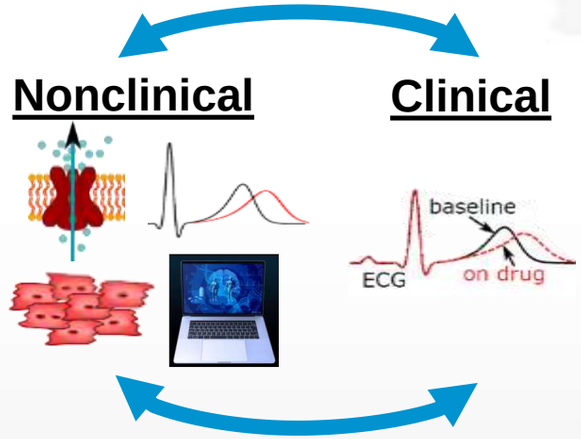
- **S7B Q&As on**
  - Integrated risk assessment
  - Best practice considerations for *in vitro* and *in vivo* assays
  - Principles of proarrhythmia models
- **E14 Q&As on use of nonclinical data to inform regulatory decision-making**
  - In late stage clinical development
  - At the time of a marketing application

New Q&As to S7B



Day 1 Presentations

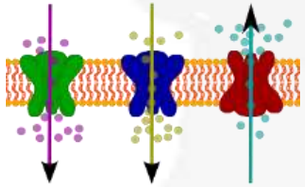
Integrated risk assessment considerations when nonclinical data are used prior to human testing **and** later in clinical development for E14 scenarios (Q&As 1.1-1.2)

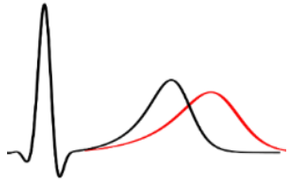


New S7B Q&As

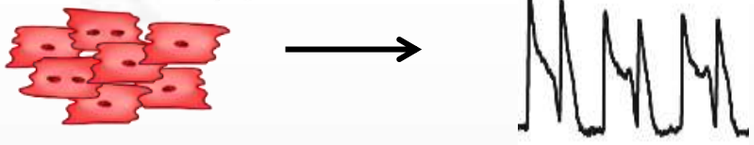
Day 2 Presentations

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

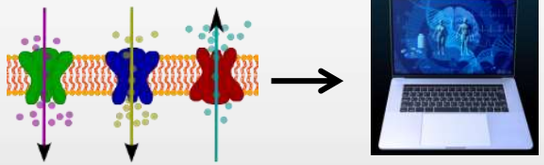




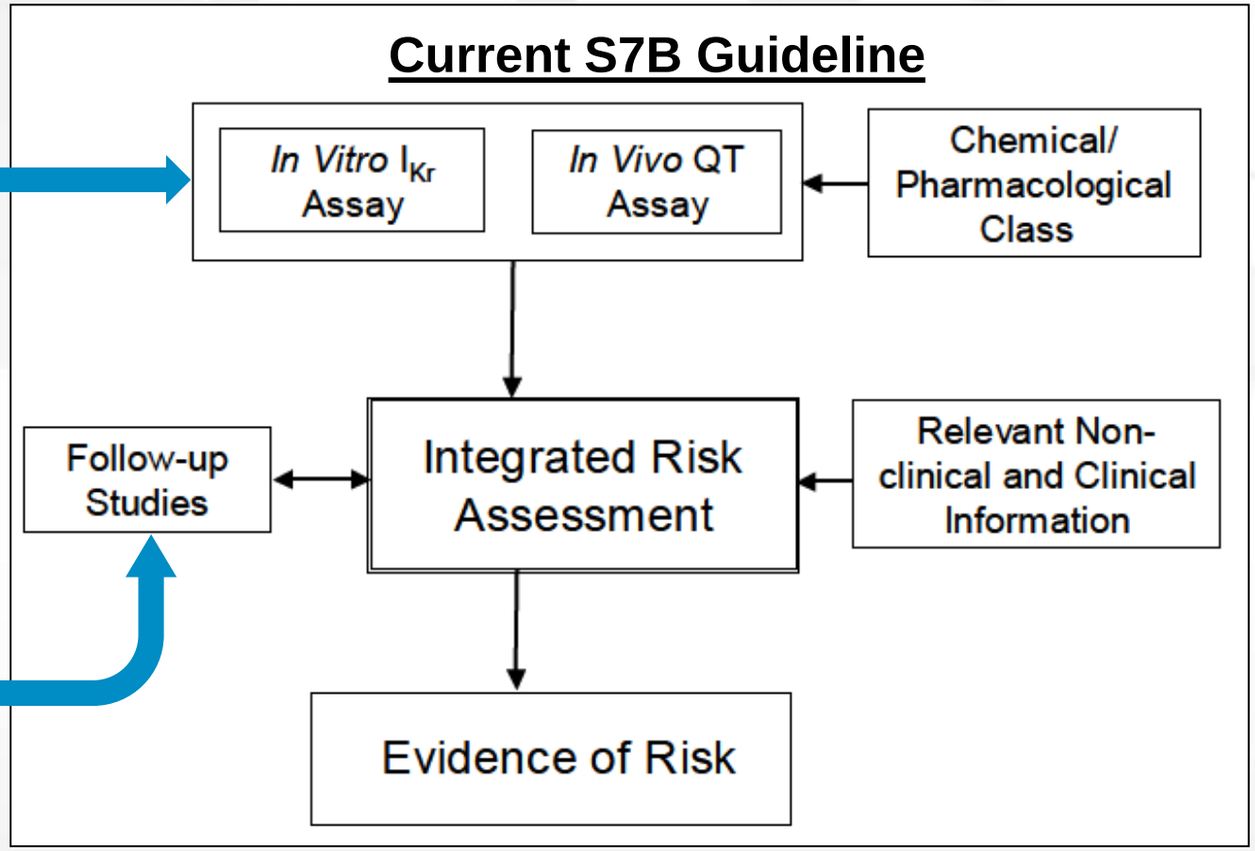
"Best practice" considerations for myocyte assays (Q&As 2.2-2.5)



Principles of proarrhythmia models (Q&As 4.1-4.3)



Model risk prediction



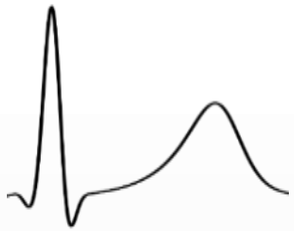
**Not intended to impact a sponsor's screening activities. Some considerations only apply when using nonclinical data for clinical scenarios under E14 Q&As 5.1 and 6.1.*

Stage 1 Q&As: Two Scenarios to Use Nonclinical Data to Inform Clinical Decision Making in New Q&As

Double negative scenario

No hERG block

No QT prolongation

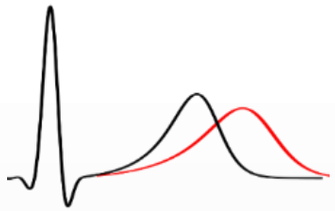


Non-double negative scenario

hERG block

and/or

QT prolongation



Revised E14 Q&A 5.1 – Nonclinical Data to Decrease the Need for TQT Studies

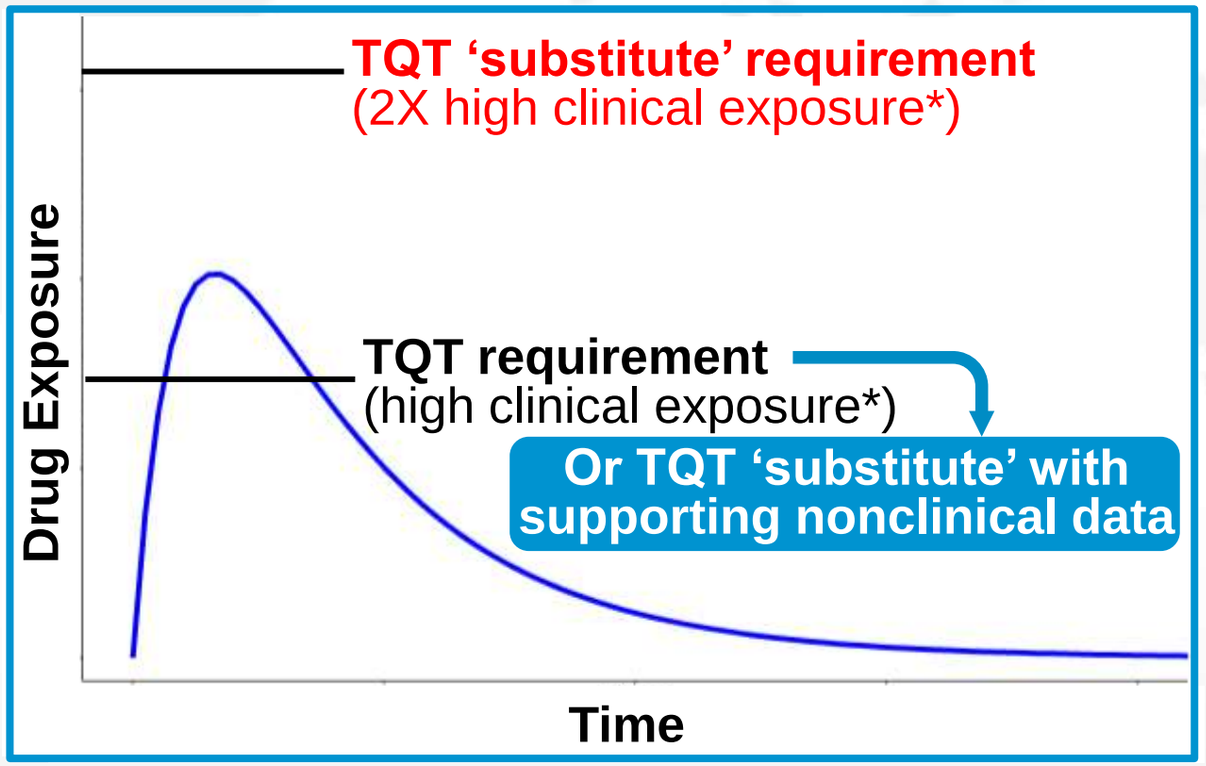
Use double-negative nonclinical data to:

- Allow for additional TQT 'substitutes' when the drug exposure in concentration-QTc analysis is not high enough to meet the current requirement

Impact:

- **Reduce the number of clinical studies in drug development**
- **Affect large number of drugs**
  - ~1/3rd of QT studies fall under Q&A 5.1
  - Only ~40% of those cover 2X high clinical exposure

Data since 2016; see Dr. Christine Garnett's presentation



*See Dr. Christine Garnett's presentation for definitions and details

Revised E14 Q&A 6.1 – Nonclinical Data to Inform Decision Making When TQT Can't Be Performed

Use double-negative nonclinical data to:

- **Inform regulatory decisions and labeling when a TQT study (or 'substitute') cannot be conducted because of**
  - Safety concerns with healthy volunteers (e.g. oncology)
  - Feasibility concerns in patients that results in lack of a positive control or inability to achieve high exposures
  - Confounded QT assessment

TQT (or 'substitute') cannot be conducted

Impact:

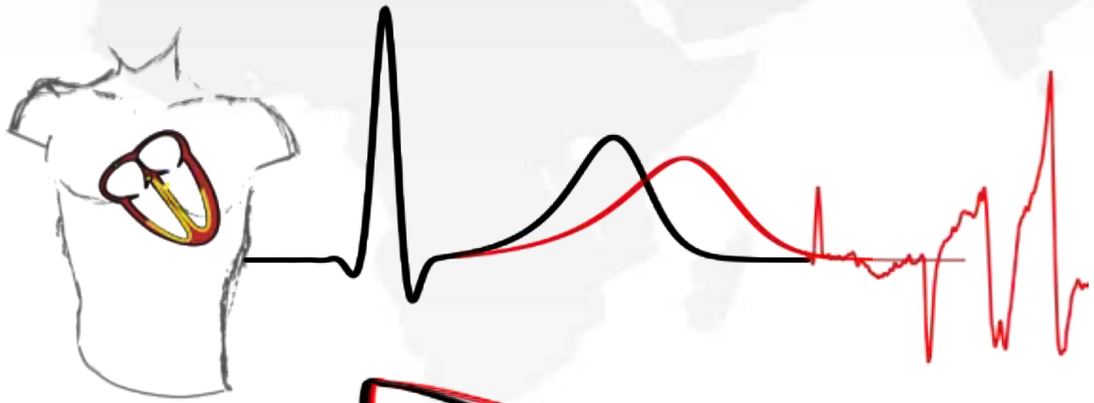
- **Change regulatory decision making and labeling**
  - Cases often result in a finding of "no large QT effects"; with new Q&A, a conclusion of low risk can be reached
- **Will affect large number of drugs**
  - ~25% of QT studies submitted to FDA fall under Q&A 6.1

Data since 2016; see Dr. Christine Garnett's presentation

"No Large QT Effects" → **Low Risk**

What About hERG Block and/or QT Prolongation?

QT prolongation

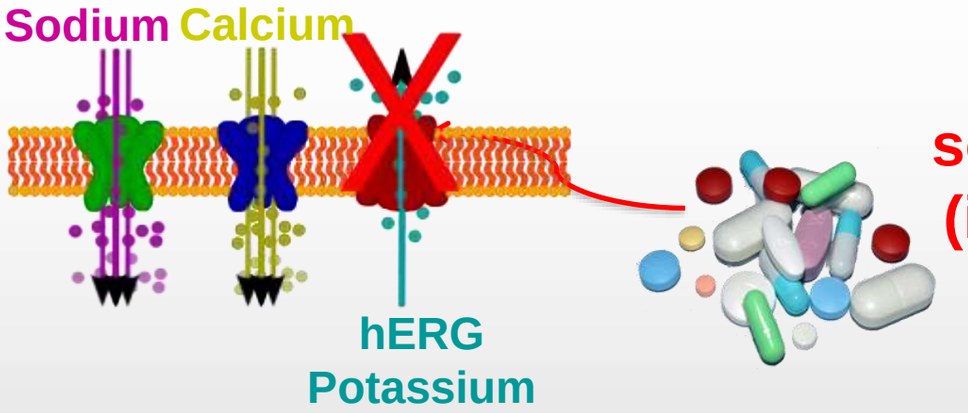


Initiate TdP

Action potential prolongation

Trigger extra beats

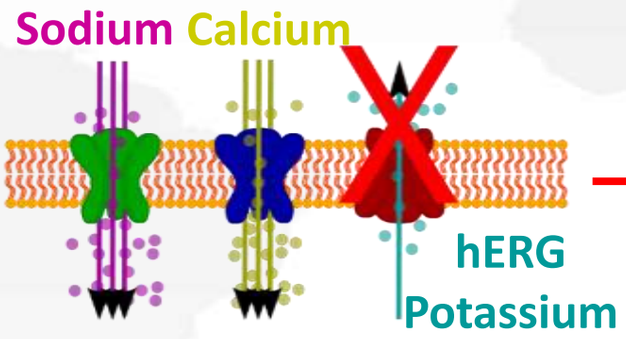
hERG channel block



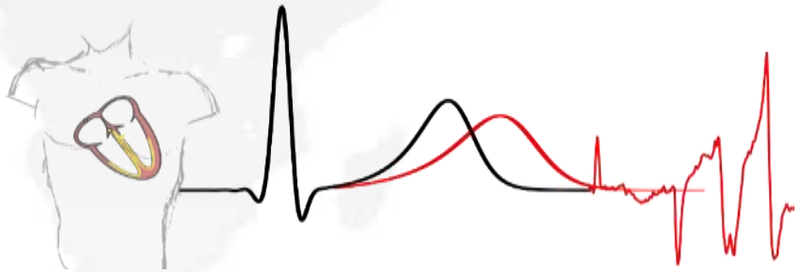
Unopposed sodium & calcium (inward currents)

Not All hERG Block/QT Prolongation Leads to TdP

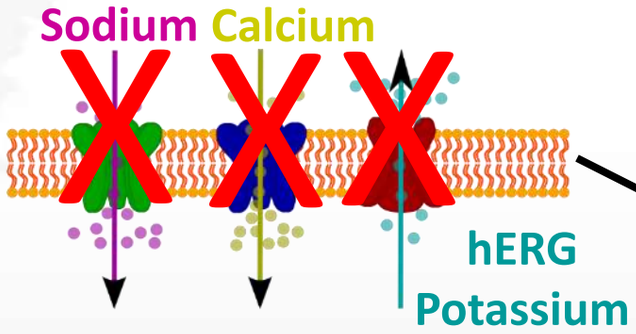
hERG Block Alone



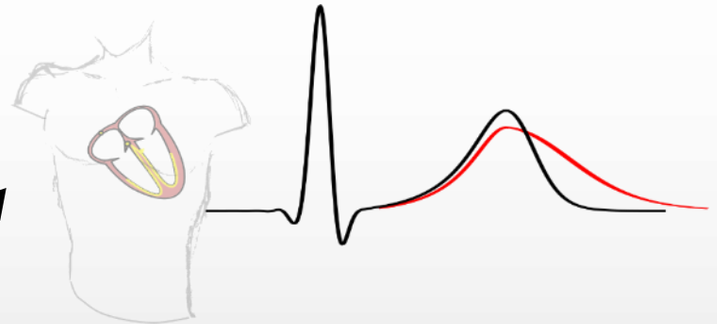
QT Prolongation, can lead to TdP



hERG + late sodium and/or calcium block



QT Prolongation, does not always lead to TdP



Non-ion channel mediated QT prolongation (e.g., autonomic effects)

Evaluate with nonclinical-clinical integrated risk assessment leveraging proarrhythmia models

Stage 1 Q&As: When hERG Block and/or QT Prolongation Is Present

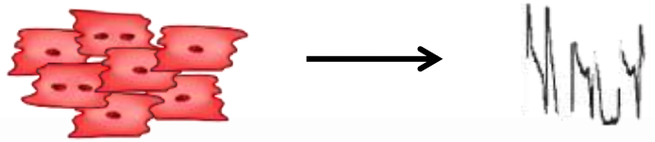
- **Follow-up studies can be performed to assess TdP risk**
  - Can contribute to design of clinical investigations and interpretation of their results
  - Subject to case-by-case evaluation

See S7B Q&As on

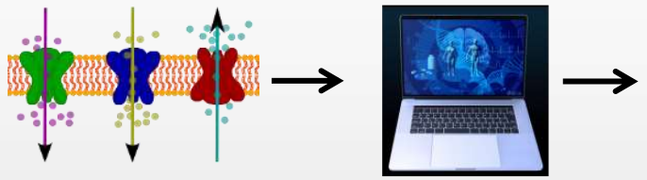
Integrated risk assessment

which references

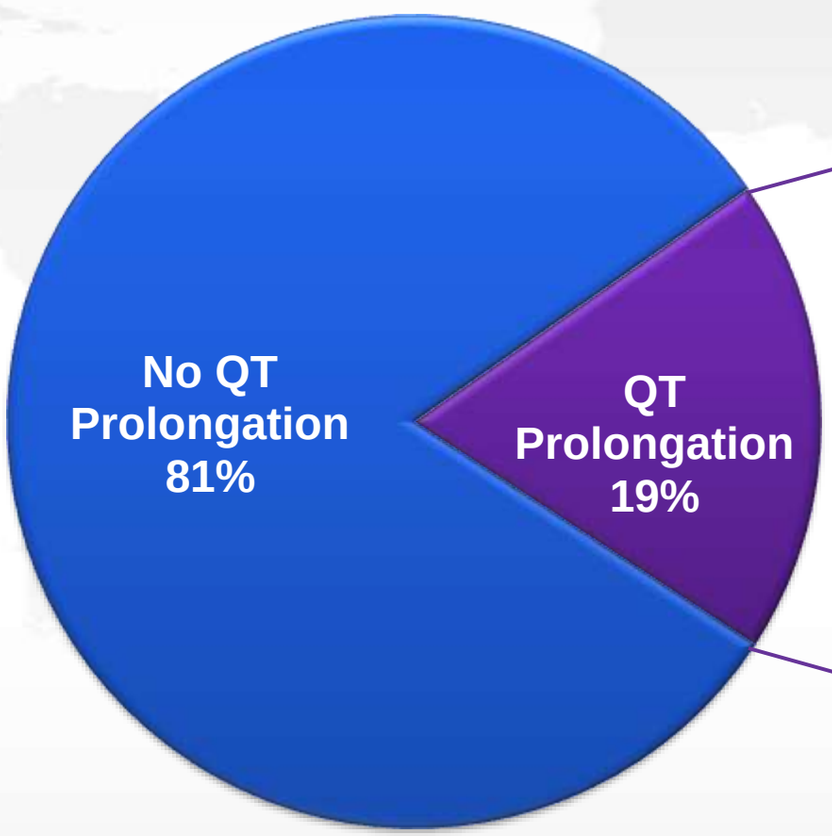
"Best practice" considerations for myocyte assays



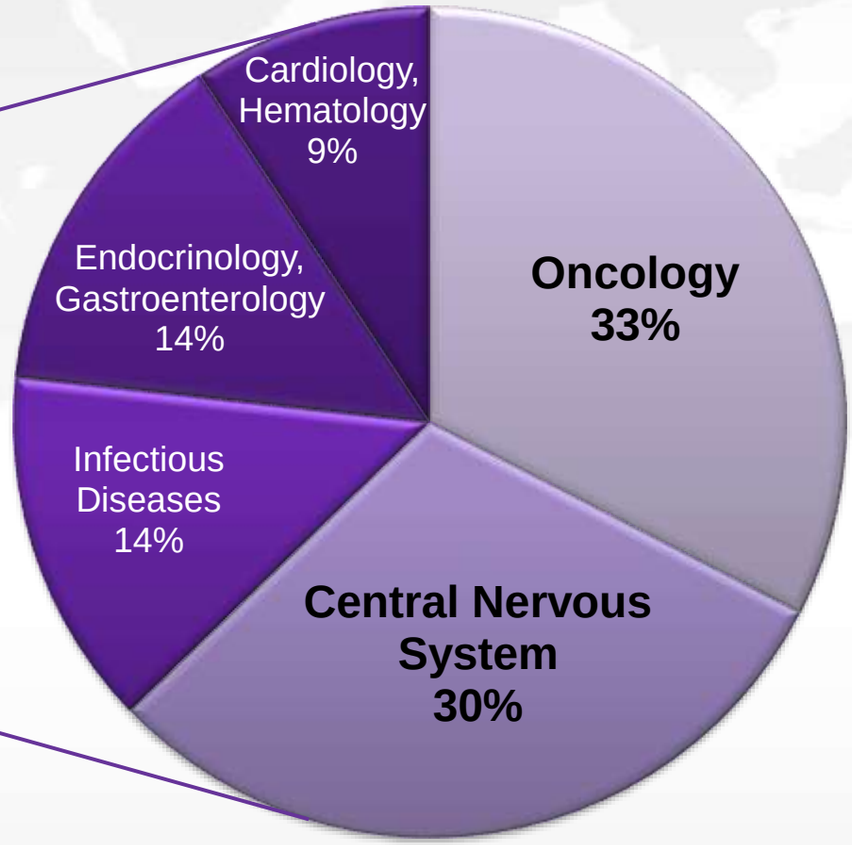
Principles of proarrhythmia models



Is QT Prolongation Still An Issue In Drug Development?



Clinical QT Study Reports to FDA (2016–2020)



Therapeutic Area of QT Prolongers

Central nervous system = neurology, psychiatry, and anesthesiology/addiction/pain

What Does E14 Currently State about QT-Prolonging Drugs?

- **ECG monitoring** (current Q&A 7.1)
  - TQT is not to assess TdP risk, but to determine what further data are warranted to assess risk
  - Intensity of ECG monitoring depends on multiple factors including characteristics of the drug (e.g., ***safety pharmacology, pharmacodynamics***)

- **Regulatory Implications/Labeling** (E14 sec. 5)
  - TdP risk might be influenced by other pharmacologic effects (e.g., other channel effects)
  - Drugs might prolong QT up to a “plateau”, above which there is no dose-dependent increase

Provides framework for stage 2 Q&As for QT-prolonging drugs on the use of safety pharmacology and pharmacodynamic data to assess TdP risk

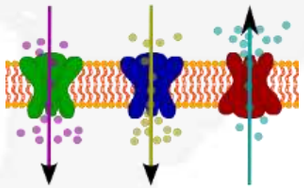
- To impact clinical development, regulatory decision making and labeling

Proposed Stage 2: Details on How Additional (New) Data Can Impact Specific Decision Making

Guidance on Follow-up Studies/Assessments → And How They Will Impact …

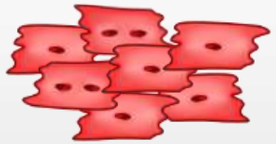
May include a combination of:

Multiple ion channels

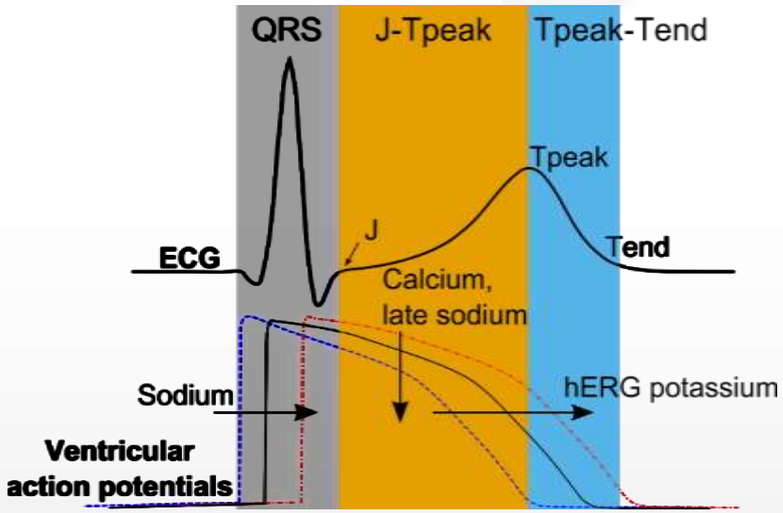


Proarrhythmia models

Assays for mechanisms of QT prolongation beyond direct hERG block



ECG biomarkers to assess concordance of *in vitro* ion channel and clinical ECG effects



Exposure-response for QTc and other ECG intervals

→

Late phase clinical trial design

(e.g., intensity of ECG monitoring, eligibility criteria, stopping rules)

Regulatory decision making at time of marketing application

Labeling

Low Risk

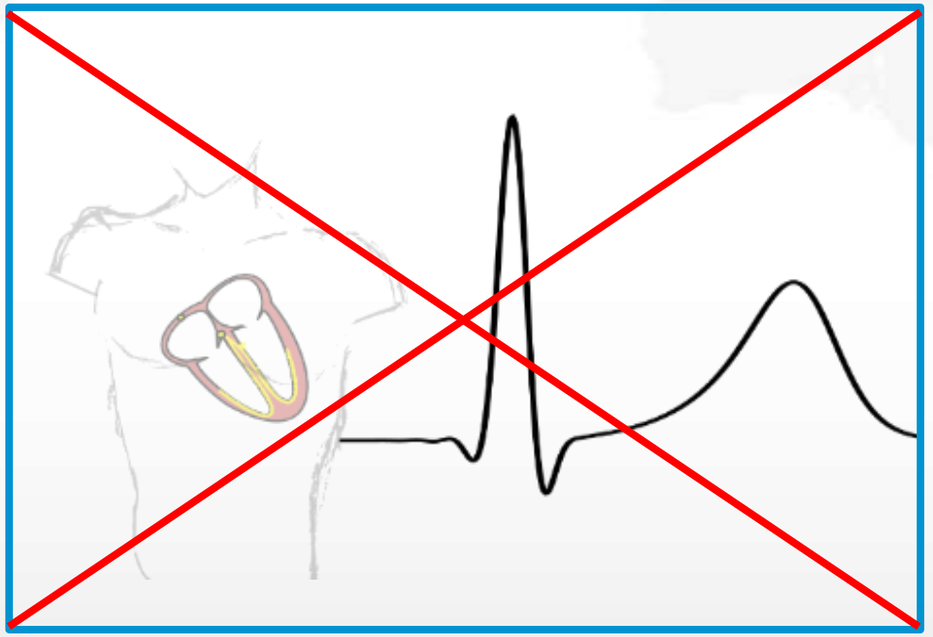
Proposed Stage 2: How to Define Low Risk Drugs That Do Not Need Detailed QT-Focused Clinical Evaluation

- **Large proteins and monoclonal antibodies already do not require detailed clinical QT evaluation due to low likelihood of ion channel interaction (E14 Q&A 6.3)**

<u>Expand to additional areas:</u>

- **Other therapeutic biotechnology products?**
  - e.g., intermediate size proteins, oligonucleotides
- **Drugs with low systemic bioavailability?**
  - e.g., dermal or ocular products
- **Other?**

Each may require different considerations



Summary of E14/S7B Working Group Activities

- **Stage 1:**
  - S7B Q&As on the integrated risk assessment, best practice considerations for *in vitro* and *in vivo* assays, and principles of proarrhythmia models
  - E14 Q&As on how to use the nonclinical data to decrease the need for TQT studies and improve regulatory decision making and labeling when a TQT study or equivalent cannot be performed

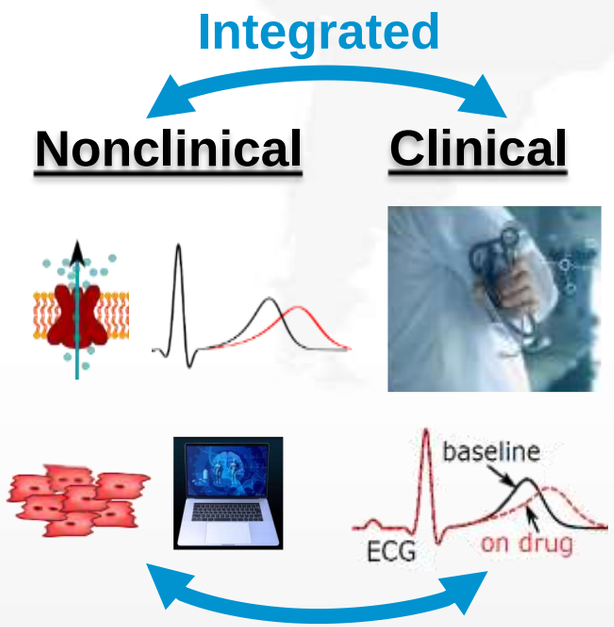
  Subsequent presentations in this webinar are on the recently-released stage 1 Q&As

- **Proposed Stage 2:**
  - How to use proarrhythmia models and ECG biomarker data to inform decision making and labeling for QT prolonging drugs
  - How to define low risk drugs that might not require detailed clinical QT assessment

  After completing stage 1 Q&As, the working group will proceed to stage 2 or make recommendations for what additional data are required

Day 1 Schedule

E14 Scenarios and Integrated Risk Assessment



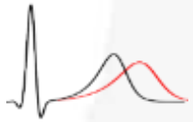
- ✓ **Background, Motivation for and Overview of the New Q&As for ICH E14 and S7B**
  - ✓ David Strauss, *FDA, United States*
- ➢ **Revised E14 Q&As and Presentation of Examples to Highlight the Impact of Nonclinical Data on Clinical Development and Interpretation**
  - Christine Garnett, *FDA, United 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*

Day 2 Schedule

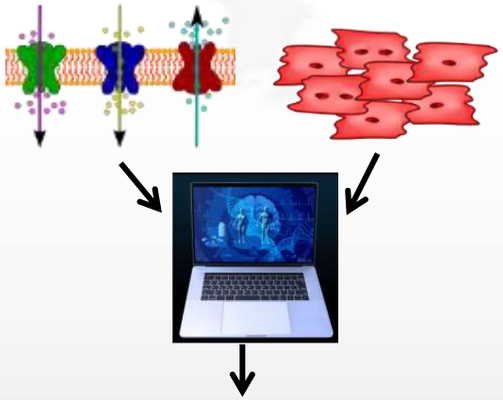
Best Practice Considerations

***In vitro* studies**

In vivo studies



Principles of Proarrhythmia Models



- **Recap of Day 1 and Introduction to Day 2**
  - Derek Leishman, *PhRMA*
- **Best Practice Considerations for *In vitro* Studies Q&As**
  - Wendy Wu, *FDA, United States* and Gary Gintant, *PhRMA*
- **Best Practice Considerations for *In vivo* QT Studies Q&As**
  - Satoshi Tsunoda, *MHLW/PMDA, Japan*
- **Principles of Proarrhythmia Models Q&As**
  - Takashi Yoshinaga, *JPMA*
- ***Discussion of Questions Received from the Q&A Pod***
  - Facilitators: Derek Leishman, *PhRMA* and David Strauss, *FDA, United States*
  - **All Speakers** and Xiaodong Zhang, *NMPA, China*; Eva Rached, *Swissmedic, Switzerland*; and Yu-Chung Chiao, *TFDA, Chinese Taipei; Katsuyoshi Chiba, JPMA*

Anticipated Timeline

Timeline	Action item / Milestone
Until November 30, 2020	Draft Q&As open for public comment
January – July 2021	Working group will review public comments, potentially update Q&As and finalize Q&As
July 2021 – January 2022	Working group will finalize technical training material and publish it on the ICH website
January 2022	Working group will provide a new timeline and/or recommendation for proceeding with stage 2 Q&As

Thank You to All ICH E14/S7B Working Group Members!

- **EC, Europe**
  - Dr. Frank Holtkamp
  - Dr. Flora Musuamba Tshinanu
  - Dr. Elke Röhrdanz
- **EFPIA**
  - Dr. Charles Benson
  - Dr. Corina Dota
  - Dr. Jean-Pierre Valentin
- **FDA, United States**
  - Dr. David Strauss
  - Dr. Christine Garnett
  - Dr. John Koerner
  - Dr. Wendy Wu
  - Dr. Zhihua Li
- **Health Canada, Canada**
  - Dr. Colette Strnadova
- **JPMA**
  - Dr. Katsuyoshi Chiba
  - Dr. Maki Ito
  - Dr. Takashi Yoshinaga
- **MHLW/PMDA, Japan**
  - Dr. Satoshi Hoshide
  - Dr. Wataru Kuga
  - Dr. Satoshi Tsunoda
  - Dr. Kaori Shinagawa
- **NMPA, China**
  - Dr. Shuiqiang Wang
  - Dr. Xiaodong Zhang
- **PhRMA**
  - Dr. Gary Gintant
  - Dr. Derek Leishman
- **Swissmedic, Switzerland**
  - Dr. Eva Rached
  - Dr. Thomas Kleppisch
- **TFDA, Chinese Taipei**
  - Dr. Yu-Chung Chiao

Thank you to Jose Vicente and Alan Knapton (FDA), Adobe Stock (stock.adobe.com) and THEW ECG database (University of Rochester) for images used in presentation.

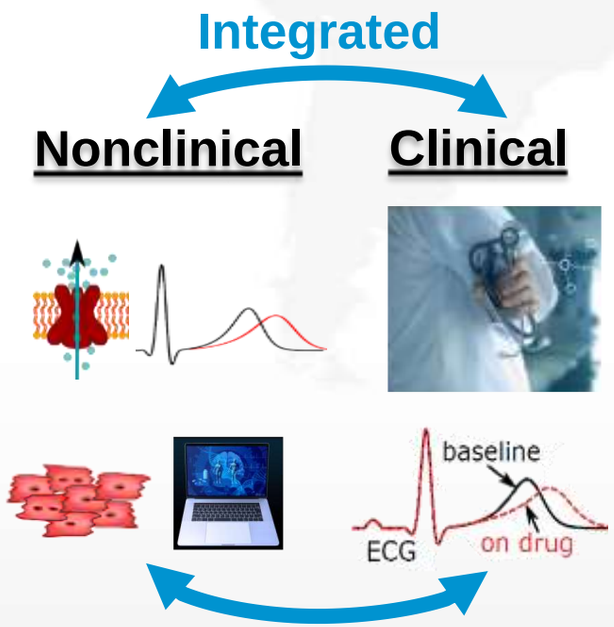
We want your feedback!

Submit your questions during the webinar via the Q&A pod

Provide official comments during public consultation periods

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*