# Update on the New ICH E14/S7B Q&As:

## Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential

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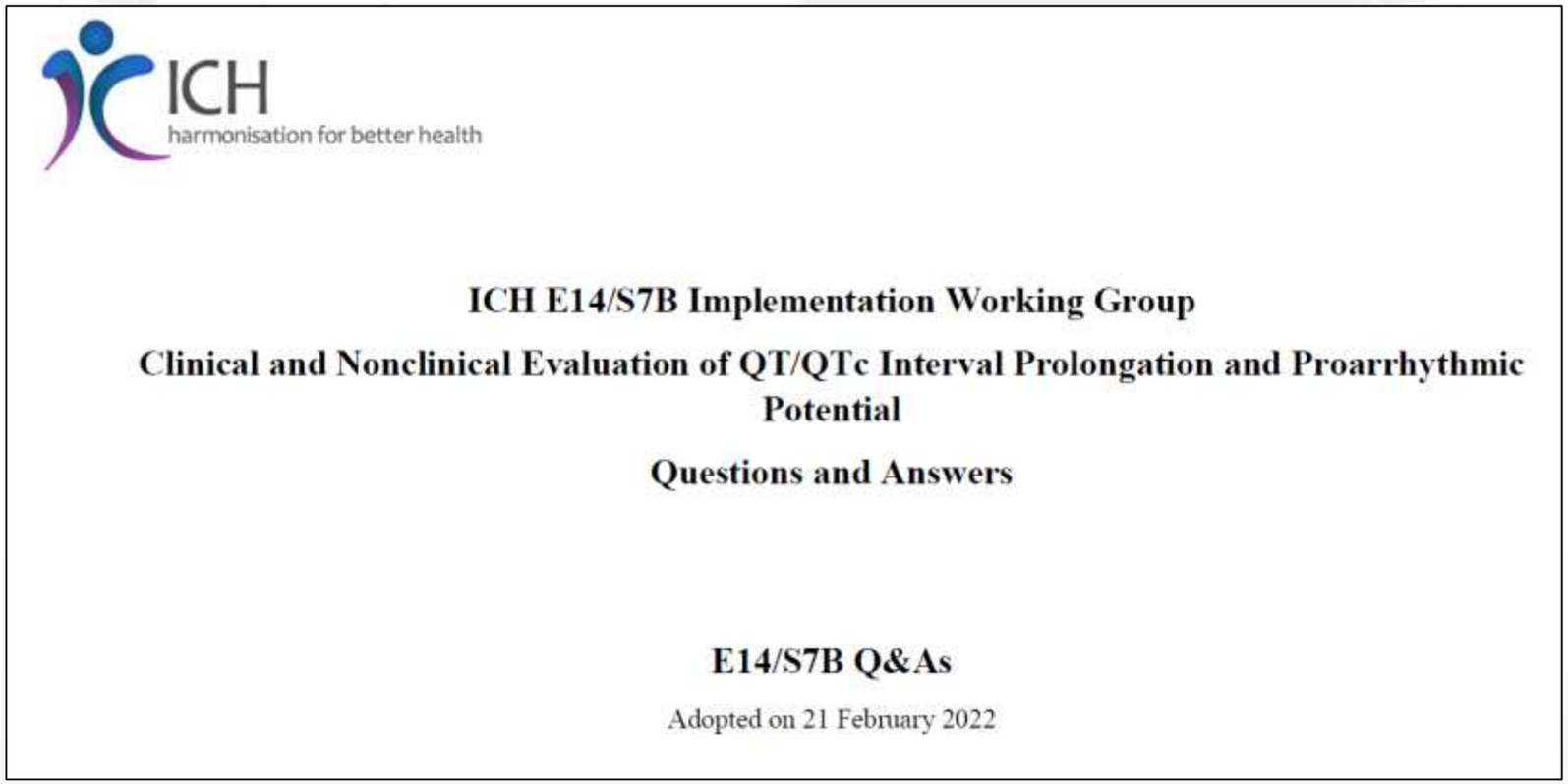
International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

# ICH E14/S7B Q&As Adopted (Step 4)!



ICH harmonisation for better health

**ICH E14/S7B Implementation Working Group**

**Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential**

**Questions and Answers**

**E14/S7B Q&As**

Adopted on 21 February 2022

https://www.ich.org/page/efficacy-guidelines#13-3

## Q&As

- E14/S7B Q&As

## Endorsed Documents

- E14/S7B Concept Paper
- E14/S7B Work Plan

## WG Presentations/ Trainings

- E14/S7B Initial Training Material ZIP
- E14/S7B Initial Training Material PDF
- E14/S7B Initial Training Material - Example Supplemental File PDF

# Clinical Problem – Drug-Induced Torsade de Pointes

**Normal**

**Torsade de Pointes (TdP)**

"Twisting of the Points"

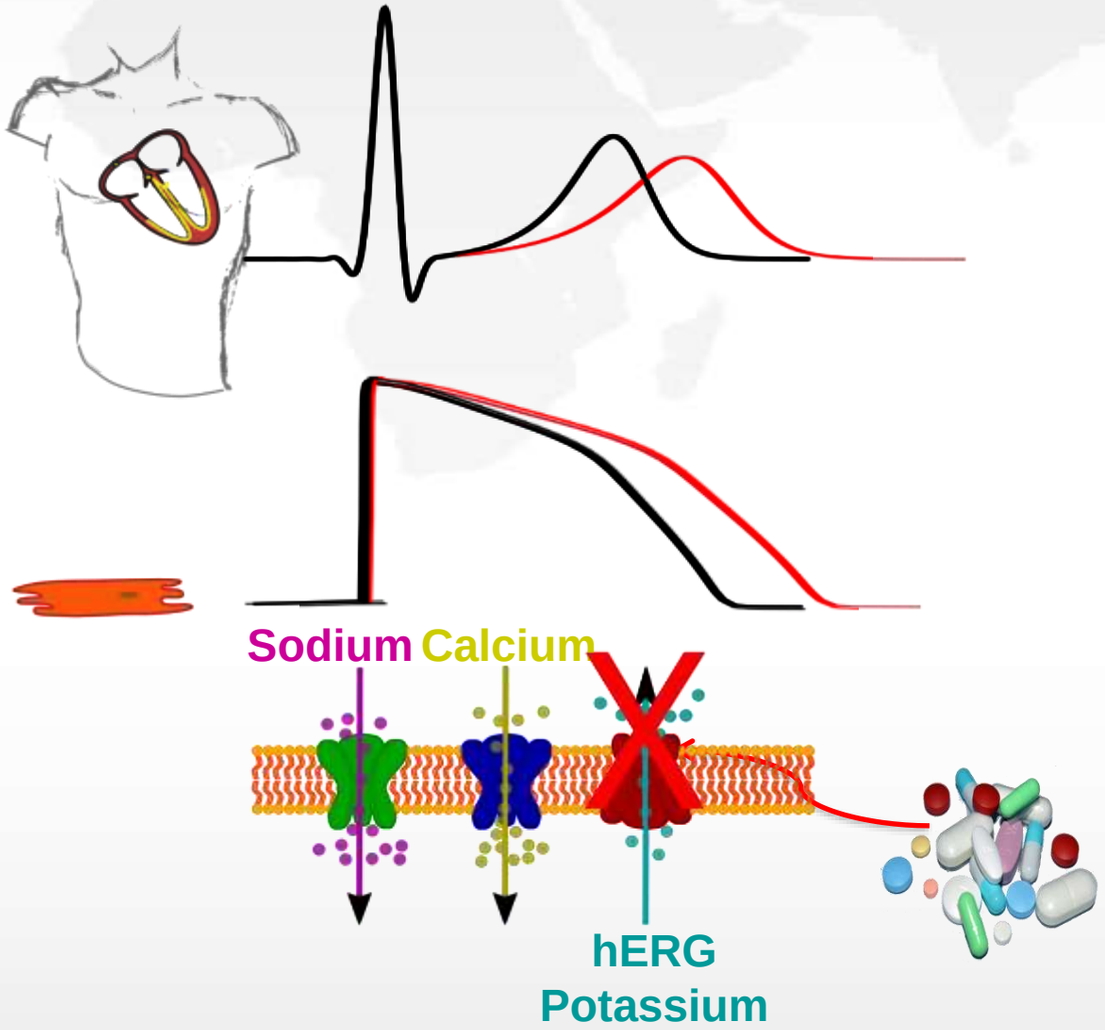
***sometimes***

# What Do TdP Drugs Have in Common?

**QT prolongation**

**Action potential prolongation**

**hERG (IKr) channel block**

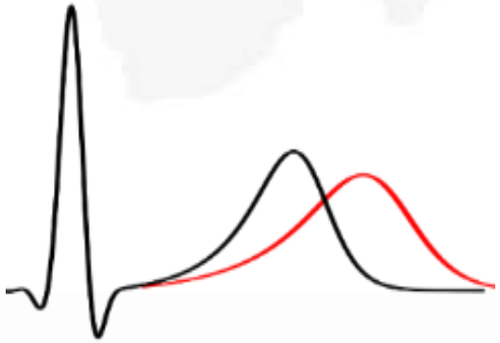


# ICH S7B Guideline: History and Impact

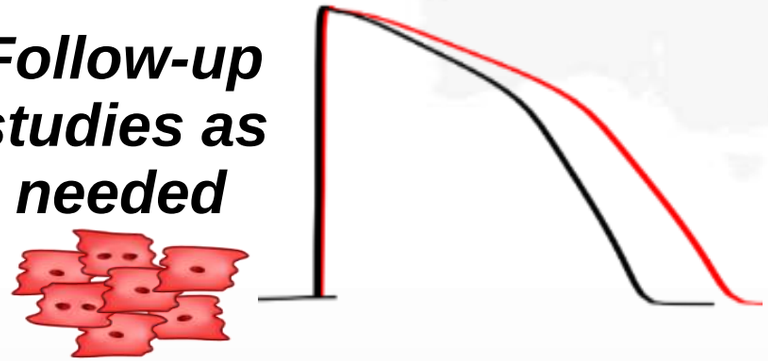
- **Established in 2005**
- **Nonclinical cardiac safety pharmacology guideline focused on assessing whether a drug:**

**Blocks hERG**

**Prolongs QT**



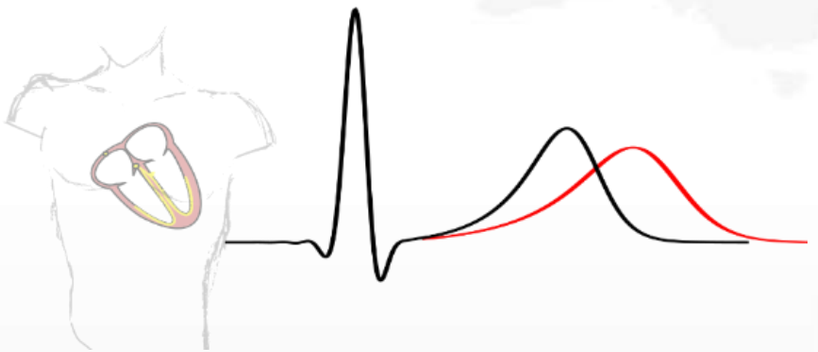
***Follow-up studies as needed***



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

# ICH E14 Guideline: History and Impact

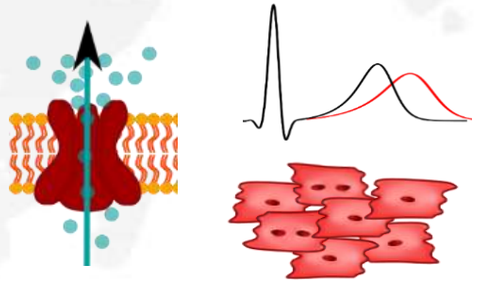
- **Established in 2005**
- **Clinical guideline describing the human 'Thorough QT' (TQT) study**
  - Established very sensitive threshold for ruling out TdP risk (~2% increase in QT – very small!)
  - Most intensive & expensive clinical pharmacology study
  - Multiple prior E14 Q&As
  - Successful in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



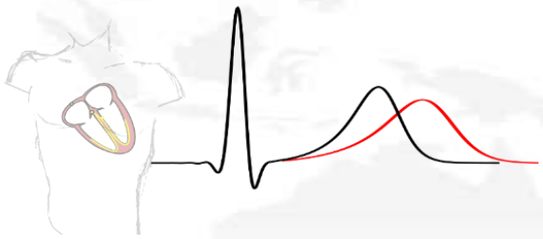
# ICH E14 & S7B: Room for Improvement

- **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**

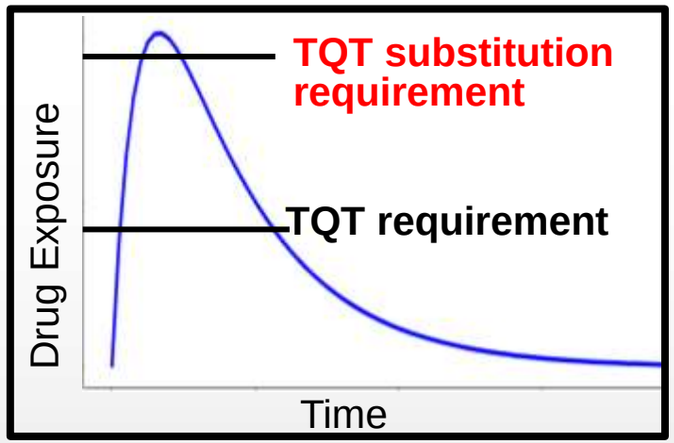


**Clinical**



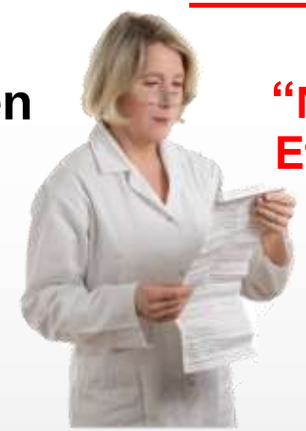
- **Prior E14 Q&As only allow for TQT study ‘substitution’** (with phase 1 concentration-QTc) **under narrow requirements**

**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**

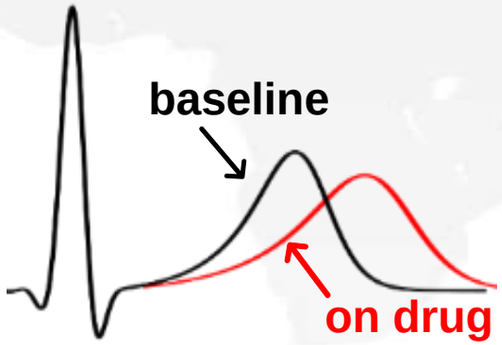


**“No Large QT Effects” label**

# ICH E14 & S7B: Room for Improvement (continued)

**E14 stated TQT goal**

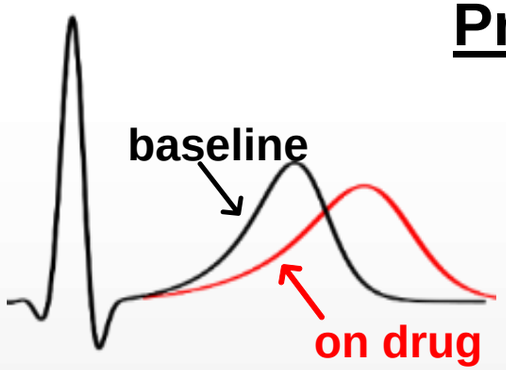
- **E14 states: TQT study is intended to inform whether ECG monitoring is required in phase 3 trials as not all QT prolonging drugs are proarrhythmic**




ECG monitoring in phase 3

**Practice**

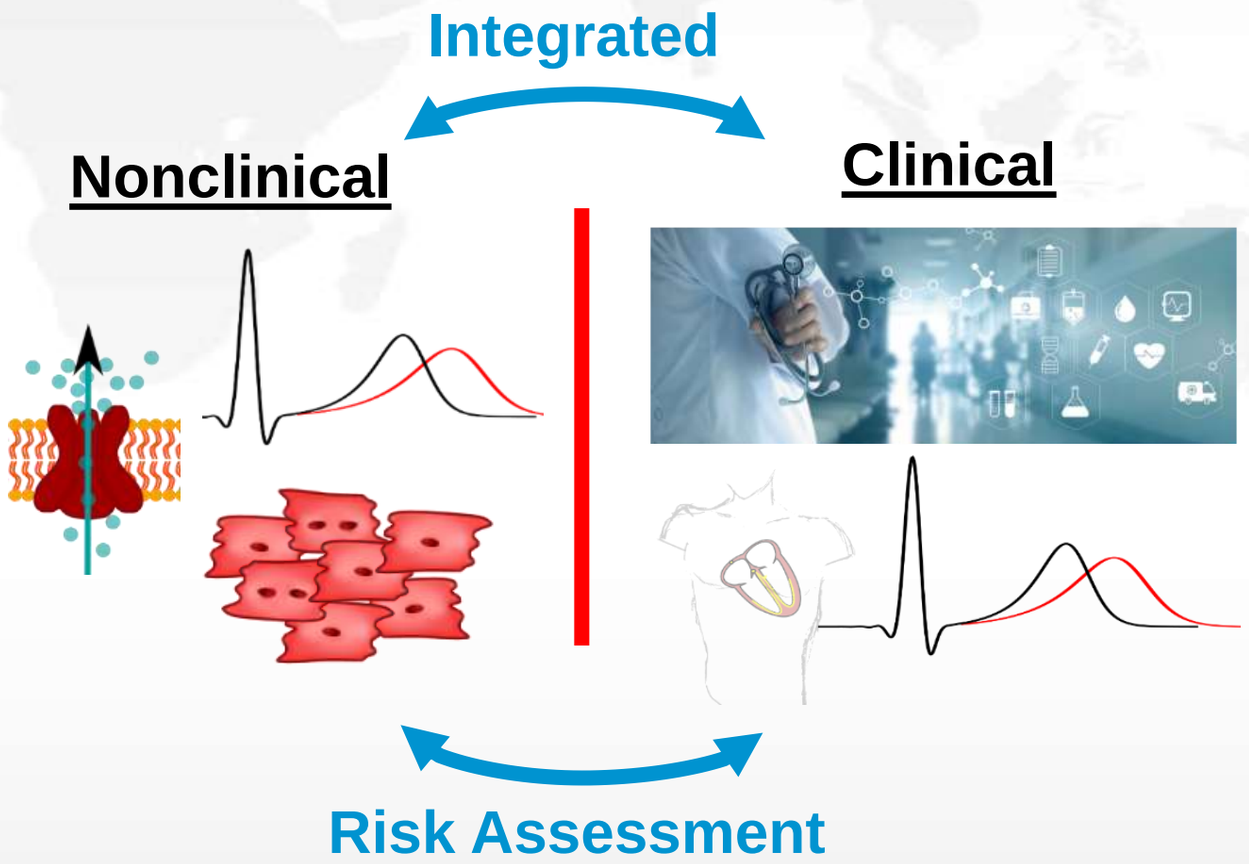
- **However: Drugs with a 'positive' hERG or QT signal are often dropped from development**




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

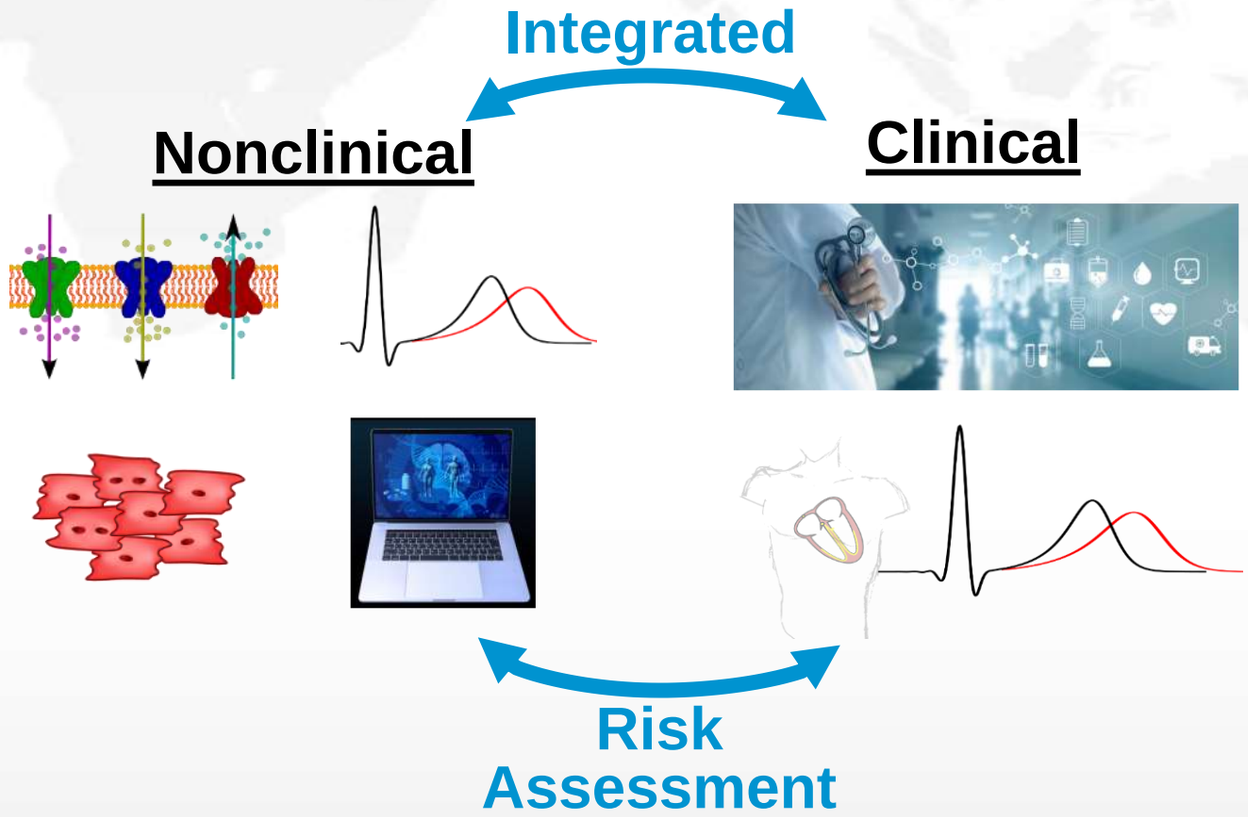
"No Large QT Effects" → Low Risk

# Strategy to Link S7B & E14

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

## Stage 1 (recently completed):

- **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

## Current S7B Guideline

*In Vitro* $I_{Kr}$ Assay

*In Vivo* QT Assay

Chemical/ Pharmacological Class

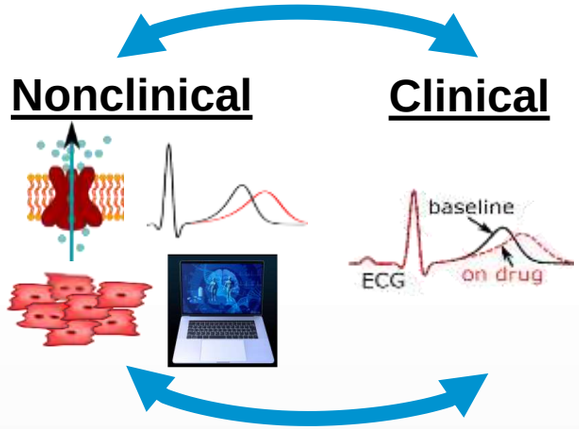
Follow-up Studies

Integrated Risk Assessment

Relevant Non-clinical and Clinical Information

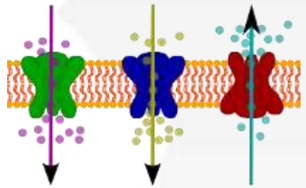
Evidence of Risk

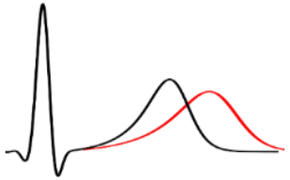
**Integrated risk assessment considerations** when nonclinical data are used prior to human testing **and** later in clinical development for E14 scenarios (Q&As 1.1-1.2)



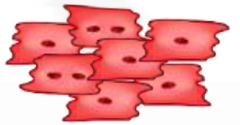
# New S7B Q&As

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

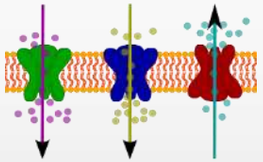




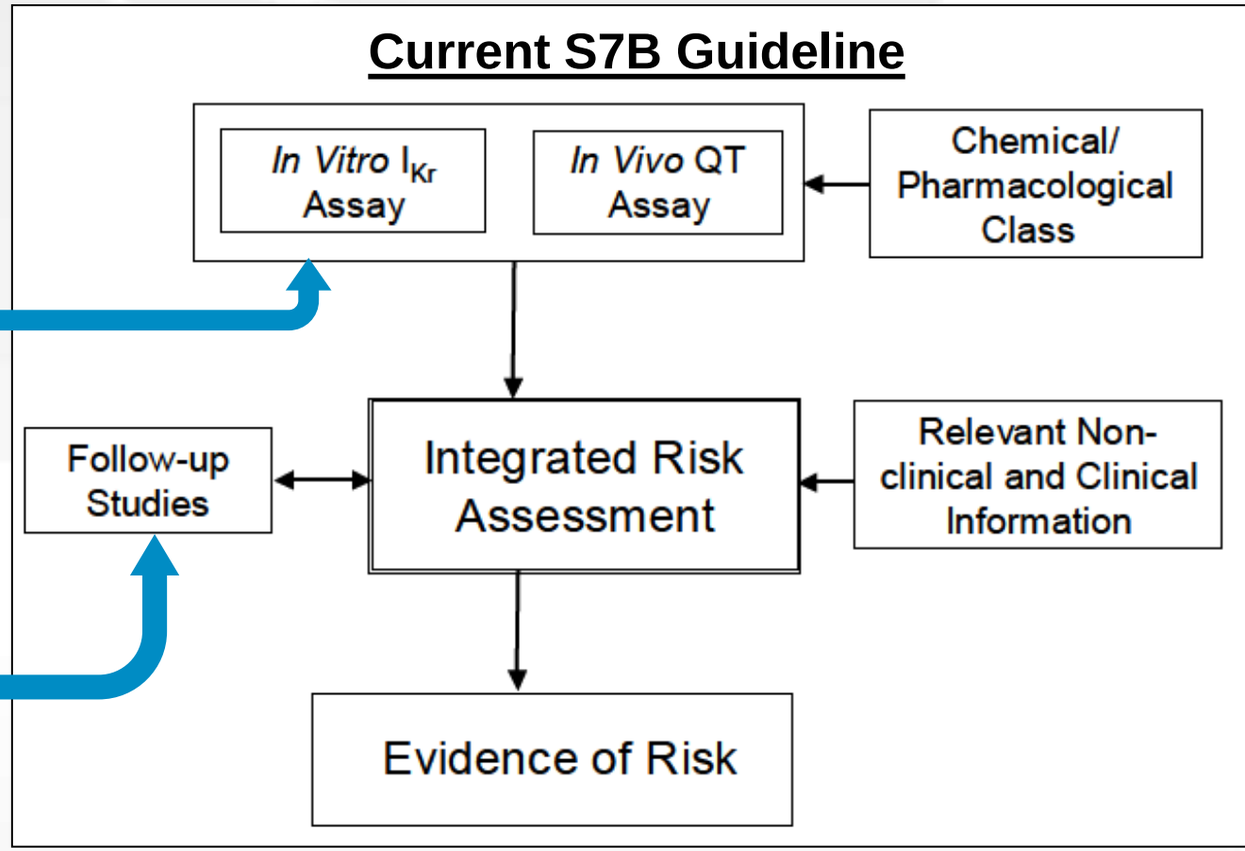
**"Best practice" considerations for myocyte assays** (Q&As 2.2-2.5)



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



**Model risk prediction**

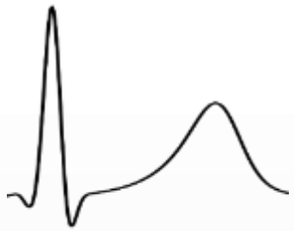


# Stage 1 Q&As: Two Scenarios to Use Nonclinical Data to Inform Clinical Decision Making in New Q&As

## Double negative scenario

**No hERG block**

**No QT prolongation**

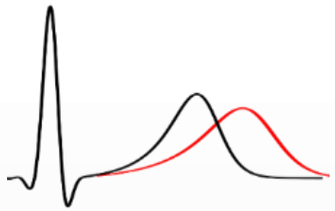


## Non-double negative scenario

**hERG block**

*and/or*

**QT prolongation**



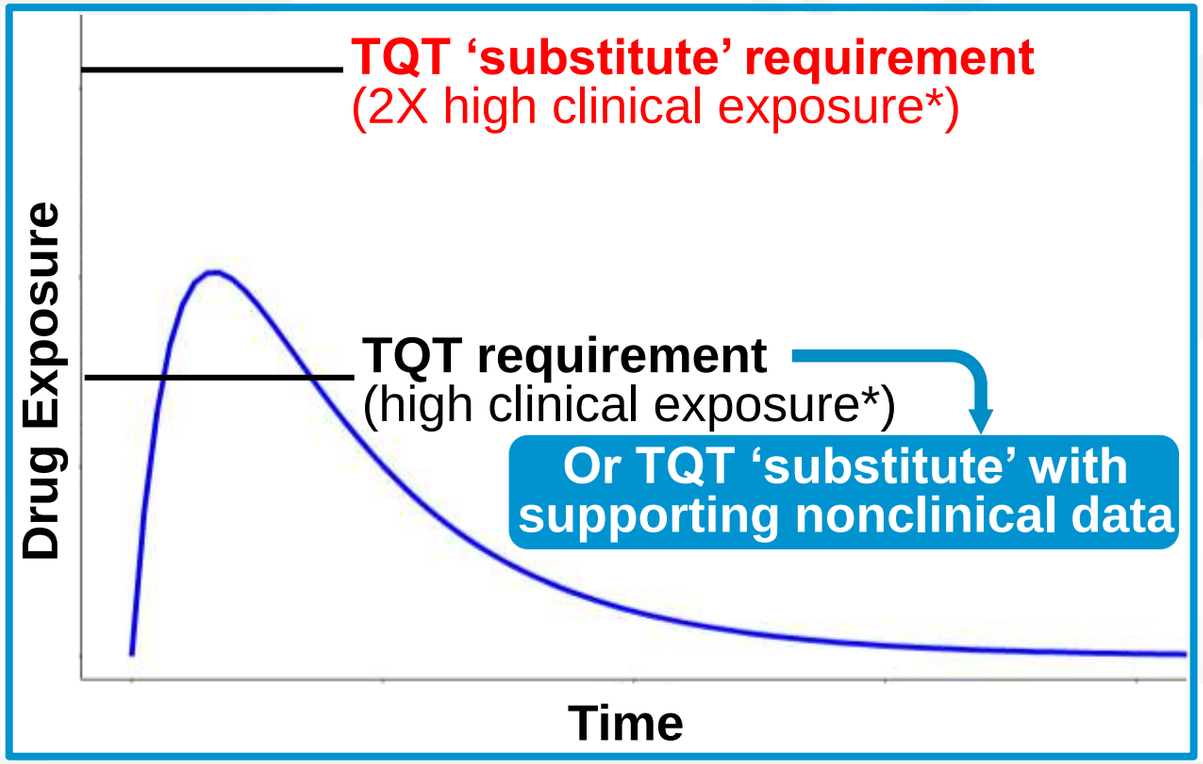
# Revised E14 Q&A 5.1

**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*



# Revised E14 Q&A 6.1

**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

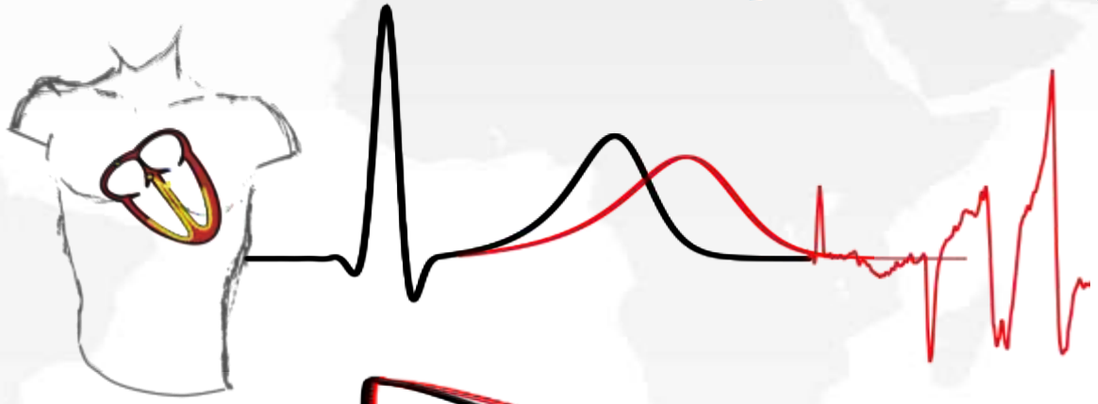
**"No Large QT Effects"** → **Low Risk**

**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*

# What About hERG Block and/or QT Prolongation?

**QT prolongation**

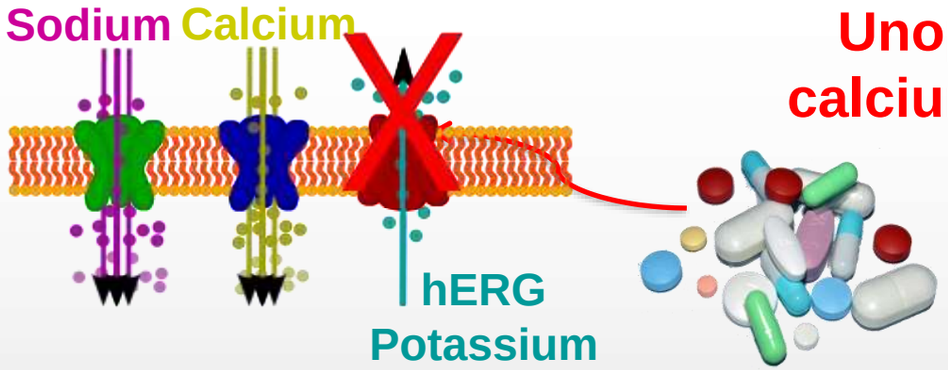


**Initiate TdP**

**Action potential prolongation**

**Trigger extra beats**

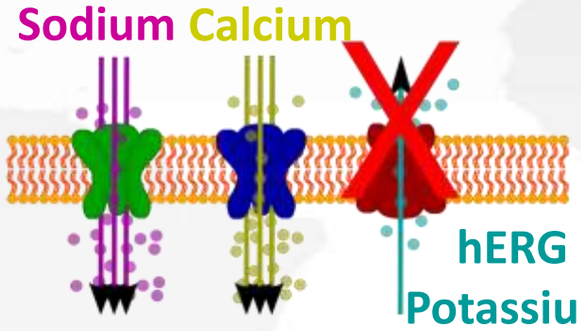
**hERG channel block**



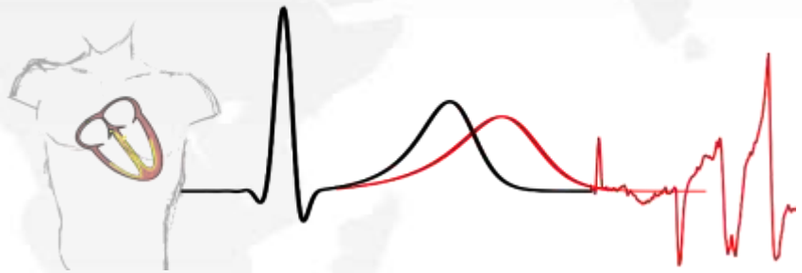

**Unopposed sodium & calcium (inward currents)**

# Not All hERG Block/QT Prolongation Leads to TdP

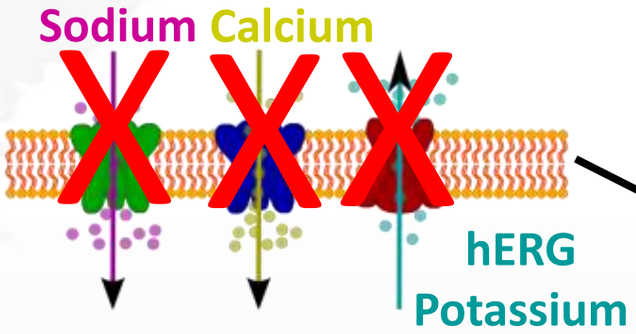
**hERG Block Alone**



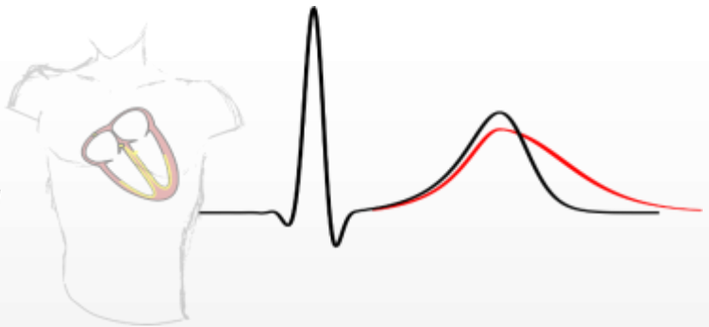

**QT Prolongation, can lead to TdP**



**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**

# When hERG Block and/or QT Prolongation Is Present

***S7B Q&As on***

**Integrated risk assessment**

*which references*

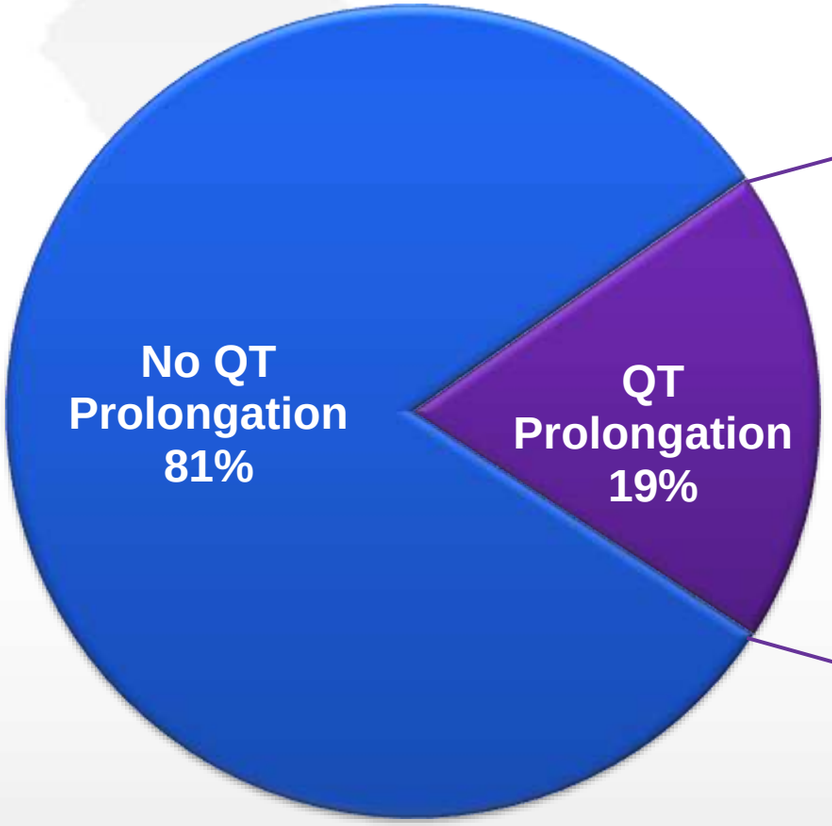
**"Best practice" considerations for myocyte assays**

**Principles of proarrhythmia models**


- **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

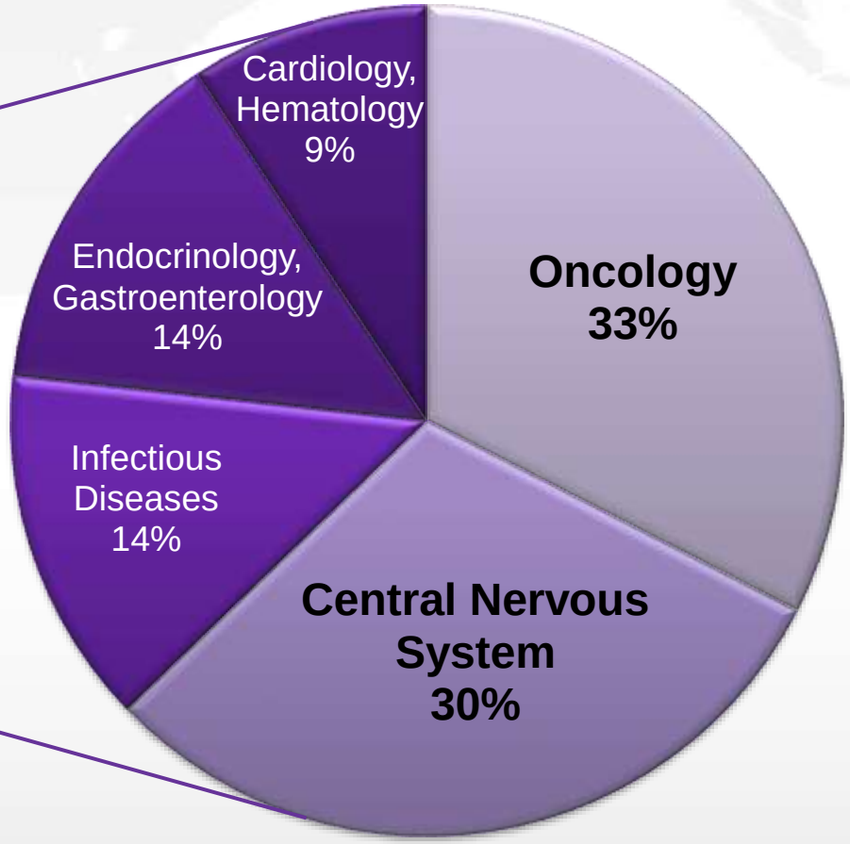
# Is QT Prolongation Still An Issue In Drug Development?

## Clinical QT Study Reports to FDA (2016–2020)




## Therapeutic Area of QT Prolongers

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

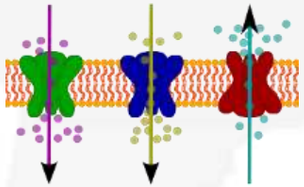


# Additional Details for QT Prolongers

## Guidance on Follow-up Studies/Assessments

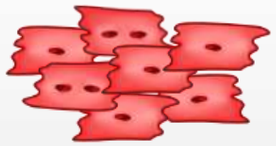
***May include a combination of:***

Multiple ion channels

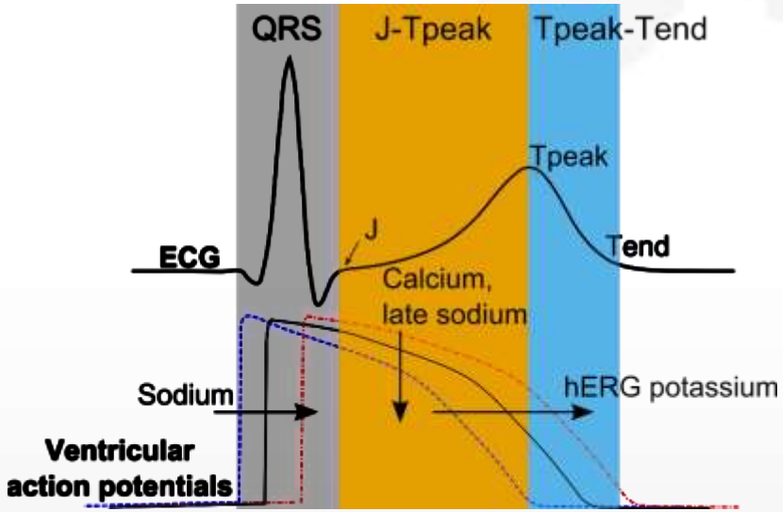


Proarrhythmia models

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

## And How They Will Impact …

**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**

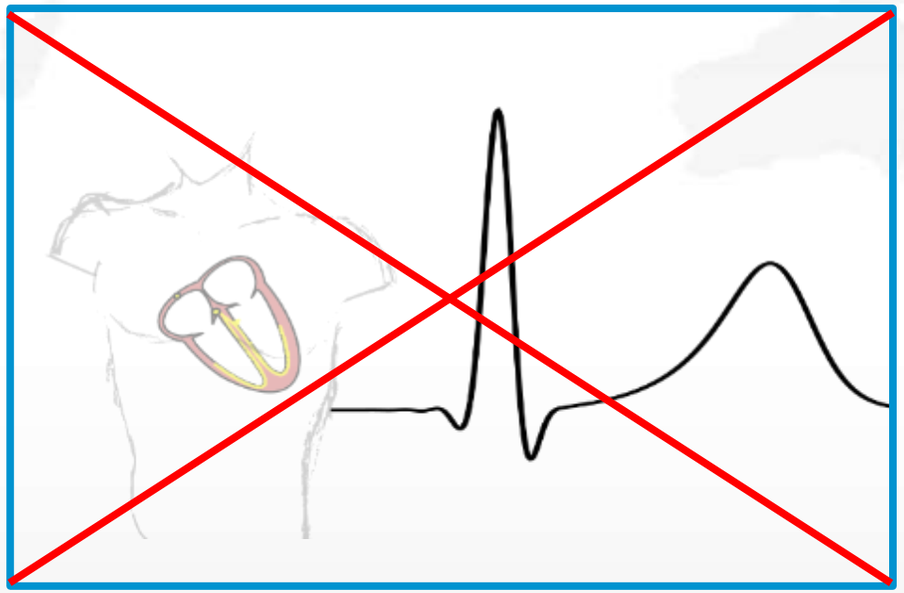
# Drugs That Don't Need Detailed QT Clinical Evaluation

- **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

- **Completed Q&As**
  - 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


- **Working group evaluating whether to pursue proposed stage 2 Q&As:**
  - 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

# Conclusions

- **While at adoption E14 suggested a QT interval evaluation independent of S7B results, both documents highlighted the need for integration of information in a manner which is informative as a totality of evidence**
- **These new E14 and S7B Q&As are directed at scenarios where nonclinical data can reduce the number of clinical studies and inform clinical regulatory decision making at the time of a marketing application**
- **These Q&As also outline best practices and principles for new and existing *in vitro* and *in silico* models that have the potential to enhance the prediction of the risk for human proarrhythmia**
- **Consideration is given to the 3R (reduce/refine/replace) principles of animal testing**

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

- **EC, Europe**
  - Dr. Frank Holtkamp
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- **EFPIA**
  - Dr. Charles Benson
  - Dr. Corina Dota
  - Dr. Jean-Pierre Valentin
- **FDA, United States**
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  - 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

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