Recap of Day 1 and Introduction to Day 2

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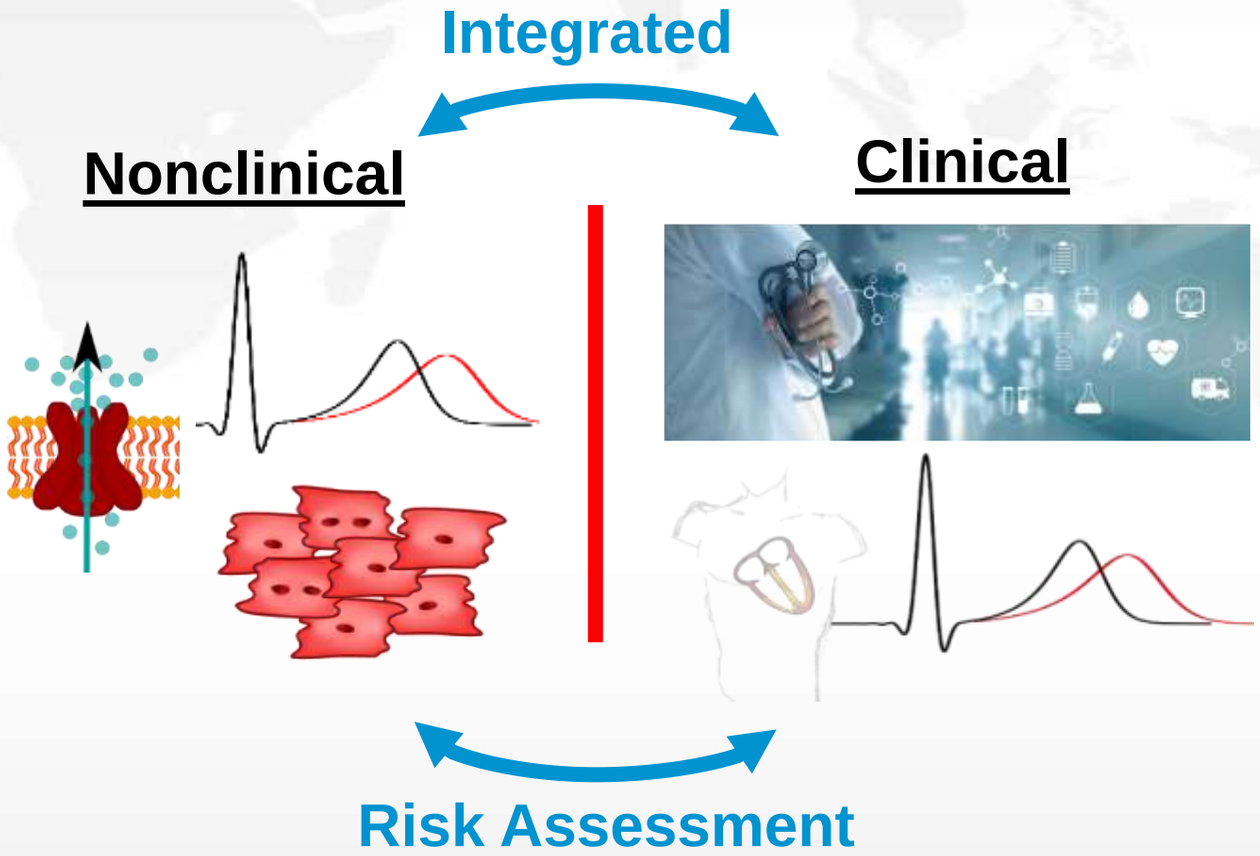
International Council for Harmonisation of Technical Requirements
for Pharmaceuticals for Human Use

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**

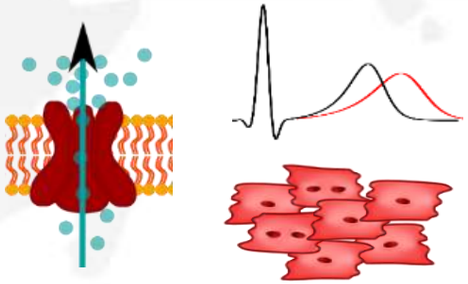


Subsequent slides reproduced from Day 1 overview presentation by David Strauss (FDA)

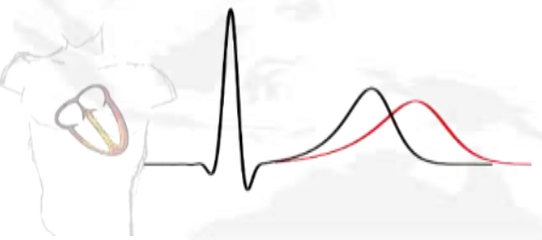
ICH E14 & S7B: Room for Improvement

- **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

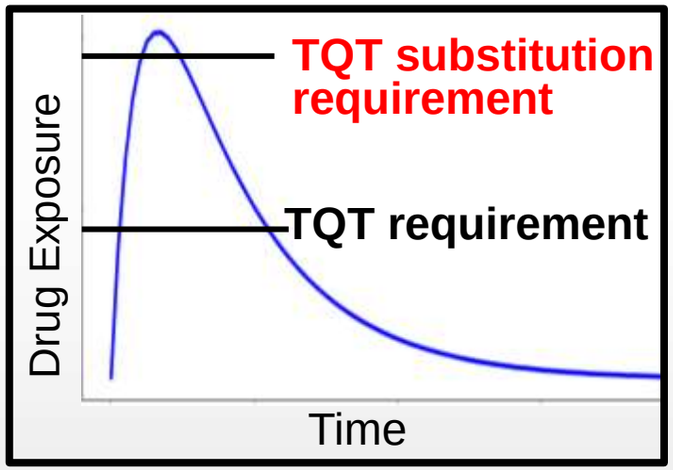


Clinical



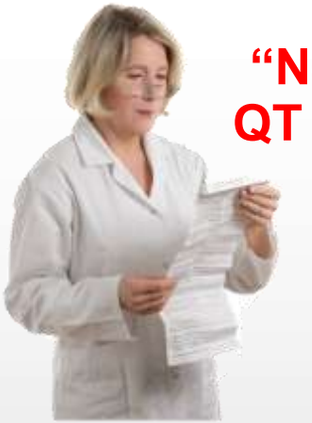
- **Prior E14 Q&As only allow for TQT study substitution under narrow requirements**

Very high exposure required!



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

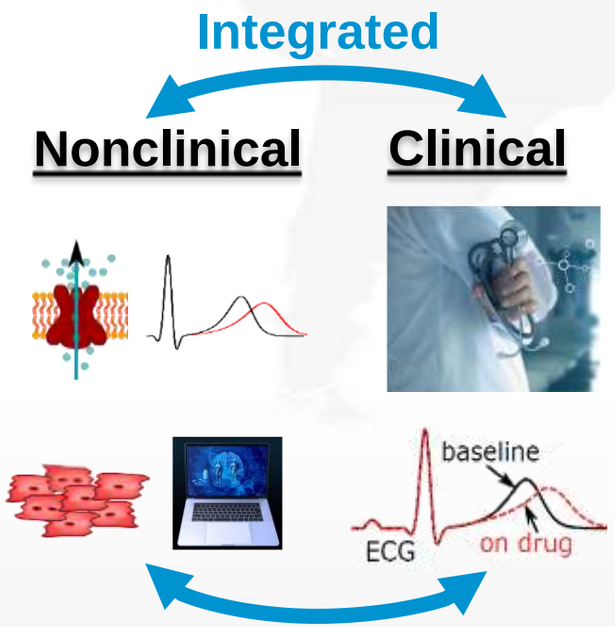
Unclear risk



"No Large QT Effects" label

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*

Value Proposition of New E14/S7B Q&As

Directed at scenarios where nonclinical data can:

Reduce number of clinical studies

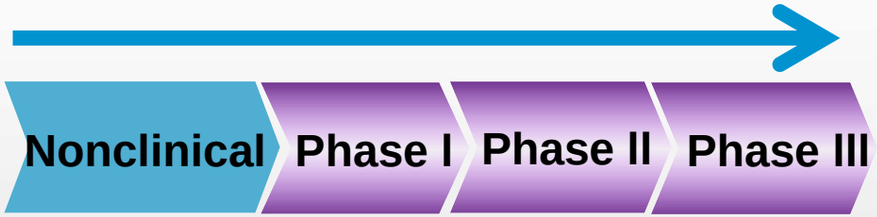
TQTs

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

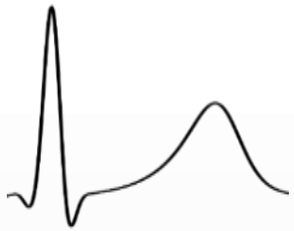
"No Large QT Effects" → Low Risk

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

Double negative scenario

No hERG block

No QT prolongation

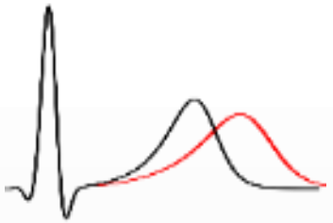


Non-double negative scenario

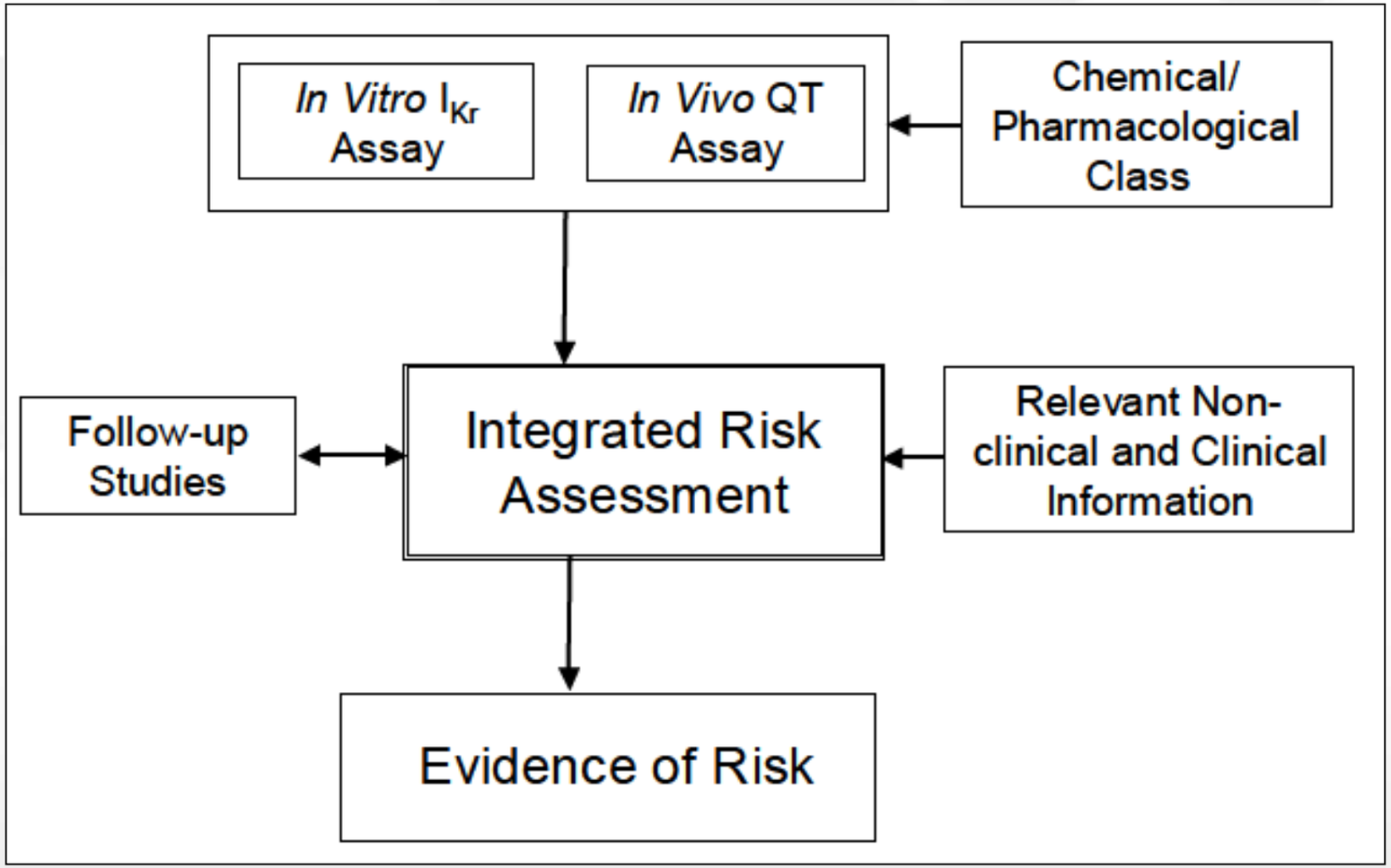
hERG block

and/or

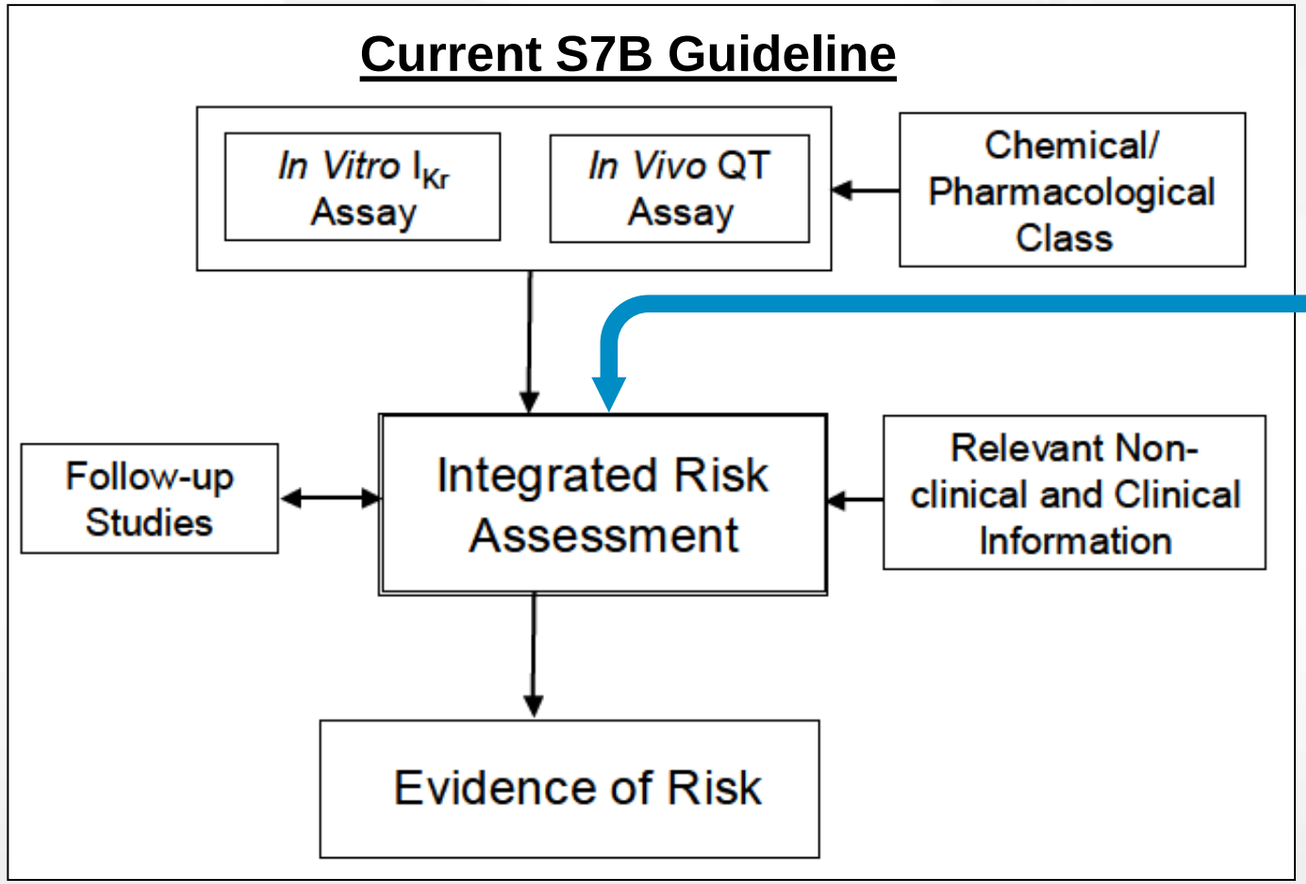
QT prolongation



Original S7B Guideline Testing Strategy Diagram

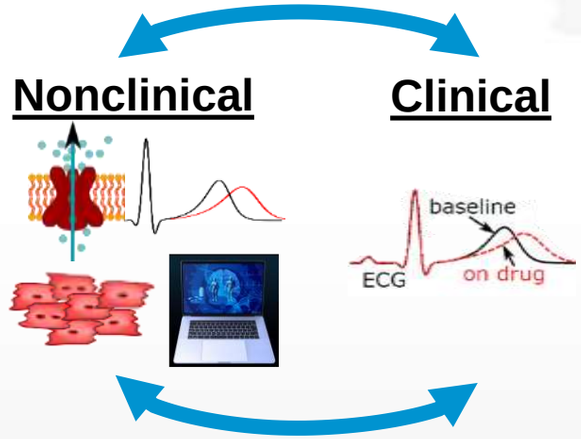


Stage 1: S7B Q&A Focus



Day 1 Presentations

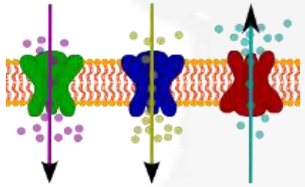
Integrated risk assessment considerations when nonclinical data is used prior to human testing **and** later in clinical development for E14 scenarios (Q&As 1.1-1.2)

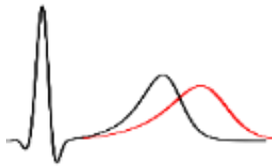


Stage 1: S7B Q&A Focus

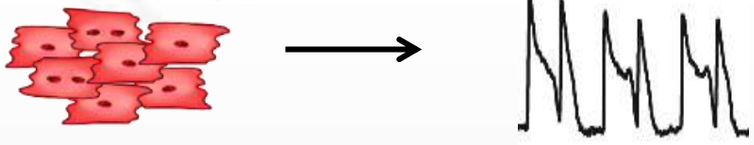
Day 2 Presentations

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

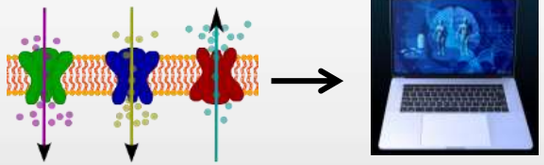




"Best practice" considerations for myocyte assays (Q&As 2.2-2.5)

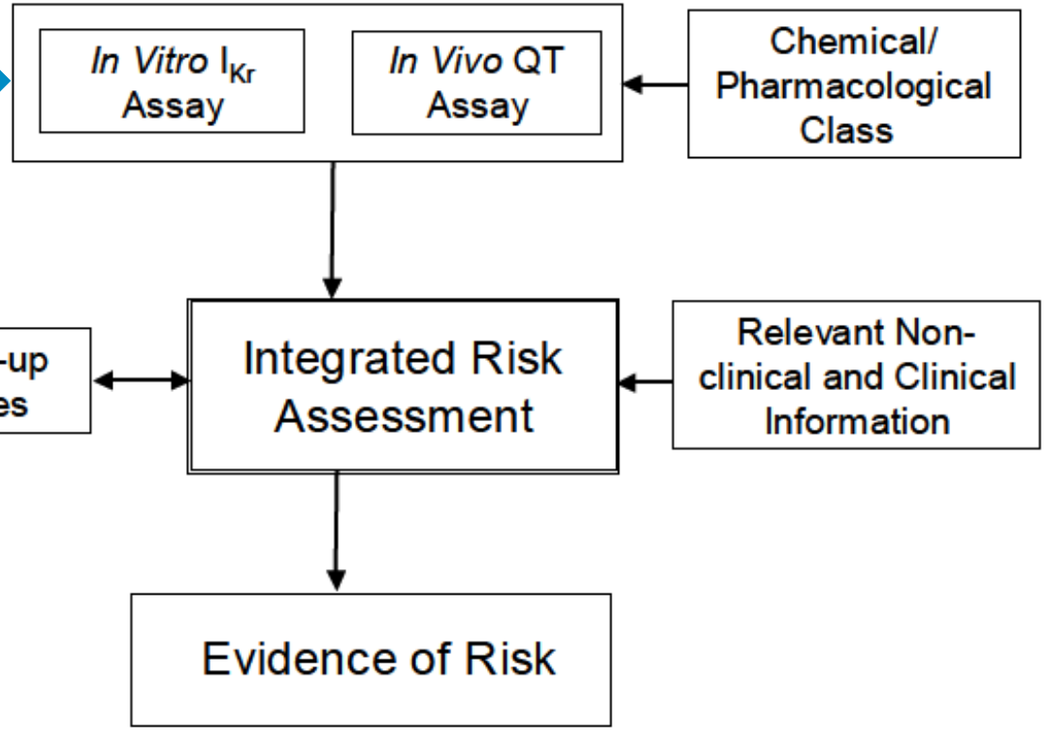


Principles of proarrhythmia models (Q&As 4.1-4.3)



Model risk prediction

Current S7B Guideline



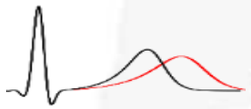
**Not intended to impact a sponsor's screening activities. Some considerations only apply when using nonclinical data for clinical scenarios under E14 Q&As 5.1 and 6.1.*

Day 2 Schedule

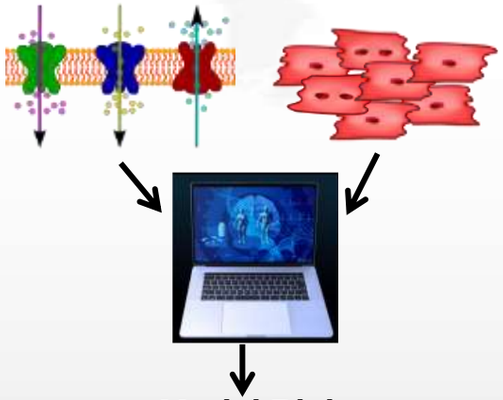
Best Practice Considerations

***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	Open for public comment
January – July 2021	Working group reviews public comments, potentially updates Q&As and finalizes Q&As
July 2021 – January 2022	Working group finalizes technical training material and publishes it on ICH website
January 2022	Working group provides new timeline and/or recommendation for proceeding with second stage Q&As

We want your feedback!

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

Provide official comments during public consultation periods

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

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