August 2020
ICH E14/S7B Implementation Working Group Update

Final Concept Paper (November 2018) available:
https://database.ich.org/sites/default/files/E14S7B_IWG_Concept_Paper.pdf

Updated Work Plan (April 2020) available:
https://database.ich.org/sites/default/files/Revised_E14%28S7B%29_IWG_Work%20Plan_2020_0430.pdf

The CiPA Steering Team is pleased to share the most recent ICH E14/S7B Implementation Working Group (IWG) update. As we have shared in the past, a concept paper was developed in November 2018 which led to the formation of a combined E14/S7B IWG to develop Questions & Answers (Q&As) to both documents. The ICH E14/S7B IWG most recently updated their Work Plan on April 30, 2020. As outlined in the Work Plan and below, in 2020 the group anticipates releasing the draft stage 1 Q&As, holding a webinar with question and answer period and opening public comment periods. When available, the Q&A document will be posted to the ICH website under the S7B and E14 tabs: https://www.ich.org/page/safety-guidelines.

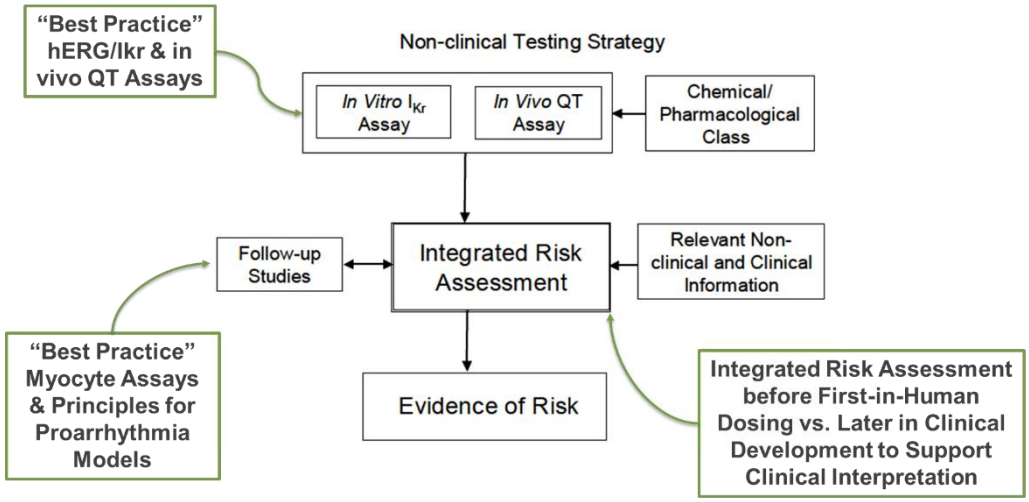
Background and Value Proposition of New/Revised E14/S7B Q&As

- 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
- Current ICH activities are directed at scenarios where the nonclinical data are informative in clinical study implementation and evaluation
  - This can reduce the number of TQT studies and improve regulatory decision making (and labelling) to more accurately determine proarrhythmic risk
  - Together this can streamline drug development, improve regulatory decision making and provide more accurate risk information to clinicians and patients in labelling

Strategy for Q&A Development to Link S7B & E14

- E14/S7B Discussion Group met in November 2018 and reached agreement on a two-stage approach to developing a combined set of Q&As; Implementation Working Group formed
- First Stage:
  - Create Q&As for S7B on in vitro and in vivo assay standardization, principles for proarrhythmia models (including in silico), and application under an integrated risk assessment for clinical situations where current E14 methodology is problematic
  - E14 Q&As on how to use the nonclinical data with clinical situations where current E14 methodology is problematic
- Second Stage:
  - Create Q&As for S7B and E14 on how to use the proarrhythmia prediction algorithms or model results, in particular for QT prolonging drugs

S7B Testing Strategy and Stage 1 Q&A Focus



E14 Scenarios to Address in Stage 1

- To supplement phase 1 ECG evaluation when exposure margin is insufficient to waive positive control in concentration response analysis
  - This will reduce the number of Thorough QT studies because more sponsors will be able to use phase 1 ECG data to conclude a drug does not prolong QT
- To supplement QT assessment when a specific study cannot be conducted because of safety concerns with healthy volunteers, for example oncology, and feasibility concerns in patients that results in lack of a positive control or inability to achieve high exposures
  - Currently these cases often result in a finding of not having large QT effects, however with nonclinical data a conclusion of low risk can be reached
- To support an uninterpretable QT assessment for a drug that causes large heart rate increases
  - This will inform on potential QT/torsade de pointes risk when clinical studies are confounded

Future Anticipated Key Milestones

Expected Future Completion Date	Milestone
June 2020	Step 1 experts sign-off
July 2020	Step 2a confirmation of consensus and Step 2b adoption of the draft guideline by ICH Assembly, followed by posting draft Q&As on ICH website
October 2020	Webinar to discuss concepts behind the Q&As and respond to audience questions
November-December 2020	Public comment periods in regulatory regions throughout the world
January-June 2021	Working group reviews public comments and finalizes Q&As for Step 3 signoff and Step 4 adoption of Q&As
July-November 2021	Finalize technical training material for first stage Q&As and finalize timeline/recommendation for second stage Q&As
January 2022	Disseminate training material on ICH website

*Above refers to first stage Q&As unless noted otherwise

Stage 2 Will Consider the Following Topics

- Non-clinical proarrhythmia models and ECG biomarker data to:
  - Help define low (or no) risk test articles that might not require detailed QT focused clinical evaluation
  - Influence the intensity of ECG monitoring in late phase trials
  - Inform the intensity of ECG monitoring and inform eligibility criteria, prohibited concomitant medications, stopping rules and considerations for labeling for drugs with uncertain proarrhythmic potential, for example QT prolongation up to 20 msec

If it is determined that enough data do not exist, the implementation working group will make recommendations for what additional data are required