Final Concept Paper

ICH S7B and E14 Q&A

Endorsed by the ICH Assembly on 15 November 2018

Type of Harmonisation Action Proposed: Q&A to S7B and E14

Statement of the Problem:

ICH S7B [1] and ICH E14[2] were finalized in May 2005 and describe non-clinical and clinical risk assessment strategies to inform the potential risk for proarrhythmia of a test substance and contribute to the design of clinical investigations. Emergent data over the past several years demonstrate that different experimental results can arise for the same compound as a function of the study conditions used in non-clinical assays. Guidance is needed regarding best practices for the design, conduct, analysis, interpretation and reporting of *in vitro*, *in silico* and *in vivo* non-clinical assays in order for these assays to influence non-clinical and clinical evaluation.

ICH E14 identifies non-clinical data as a factor that can be used to reduce the need for a TQT study (Sec. 2.1). Since the implementation of E14, there is no consensus on how non-clinical data can be used to influence the design and/or interpretation of a clinical QT study. There are several clinical scenarios that could benefit from high quality non-clinical data such as clinical QT assessments that are confounded by issues like heart rate changes, inability to test a sufficiently high multiple of the clinically relevant exposure to waive the positive control (Q&A 5.1), and when a TQT study is not feasible in healthy volunteers (Q&A 6.1).

ICH S7B recommends Follow-up Studies (Sec. 2.3.5) to inform the integrated risk assessment if a test articles blocks the $hK_V11.1$ IKr current (hERG) or prolongs the QT interval. These could include the test article effects on additional ionic currents, and the use of *in vitro* and *in vivo* assays. Newer assays and technologies such as *in silico* ventricular models, and human primary and induced pluripotent stem cell-derived cardiomyocytes, can provide insights into the relative proarrhythmic liability of test articles. Guidance is needed on when and how these novel approaches play a role in determining the proarrhythmic risk to inform clinical development.

Issues to be Resolved:

We propose two sequential stages of Q&A as detailed below. This two-stage strategy will allow for more rapid impact of novel approaches on S7B and subsequently E14 for evolving drug candidates, enabling a more efficient, comprehensive and mechanism driven process. The objective of the first stage of the proposed harmonisation work is to provide clarity on how to standardize assays such as

[1] The Non-clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation by Human Pharmaceuticals).

[2] The Clinical Evaluation Of QT/QTc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs E14

multi-ion channel assays, *in silico* models, *in vitro* human primary and induced pluripotent cardiomyocyte assays and *in vivo* evaluation, and apply these learnings to guide predictions and subsequent clinical assessment. These efforts will provide a customizable non-clinical strategy that is more informative for clinical development.

Stage 1:

Create Q&A(s) for S7B and E14 on *in vitro*, *in silico* and *in vivo* assay standardization and application, while considering the impact of these recommendations on clinical situations where current E14 methodology is problematic. For example, clinical QT assessments that are confounded by issues such as heart rate changes, inability to test a supratherapeutic concentration, and absence of a placebo group, etc. (see 'Proposed Q&As' below). Write Q&A for S7B on principles for proarrthymia risk prediction models.

Stage 2:

Create Q&A(s) for S7B and E14 on how to use the proarrythmia prediction algorithms or model results (see 'Proposed Q&As' below).

The following are examples of the issues likely to be addressed in S7B Q&A(s).

- Experimental protocol standardization considerations avoiding inconsistencies and pitfalls in voltage clamp protocols, *in silico* model use and interpretation of *in vitro* human myocyte studies, for example, defining experimental conditions (including best practice), data quality and reporting standards
- General principles for proarrhythmia models, metrics to be used for proarrhythmic prediction, and implementation of the models (will include examples)

Guidance would be provided on how these studies can inform clinical trial design and interpretation of ECG and/or adverse event data (e.g., biological plausibility considerations in causality assessments). Recommendations regarding the use of human cardiomyocytes for the assessment of electrophysiologic effects of drugs as an alternative to the currently listed animal derived single- and multicellular preparations would reduce unnecessary animal use.

In Stage 1, we foresee addressing the following potential scenarios in one or more E14 Q&As on how non-clinical data could be used:

- To supplement phase 1 ECG evaluation when the exposure margin is insufficient to waive positive control in the concentration response analysis.
- To support an uninterpretable QT assessment for a drug that causes large heart rate increases (e.g., >20 beats/minute).
- To supplement the QT assessment when a specific study cannot be conducted because of safety concerns with healthy volunteers, for example oncology, and feasibility concerns in patients.

In Stage 2 we will consider, the following topics pending sufficient data are available to support the revision of E14 Q&A additions.

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 concominant medications, stopping rules and considerations for labeling for drugs with uncertain proarrhythmic potential, for example QT prolongation in the range of 5-20 ms.

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

Type of Implementation Working Group Recommended:

Since implementation of ICH S7B and E14 in 2005, there have been multiple Q&As developed for E14. Thus, the ICH E14 working groups have consisted of clinical experts with detailed knowledge of thorough QT studies and concentration-QT modeling. The current proposed Q&As focus on non-clinical *in vitro* and *in silico* methods. In addition to retaining clinical expertise, additional experts in the following areas should contribute to the IWG: (1) the cellular electrophysiological mechanisms of TdP initiation, (2) the ability to interpret patch clamp drug block data using *in vitro* cell lines with heterologous expression of ion channels and/or *in vitro* cardiomyocytes, (3) developing or interpreting electrophysiological computer models. Since non-clinical assays may have an impact on how to perform early clinical studies and in the interpretation of clinical study results, it is also important to include clinical expertise on the IWG.

Proposed Timeline:

Nov. 2018	Finalize Concept Paper and detailed work plan for IWG
Dec. 2018-June 2019	Refine scope of first stage Q&As for S7B and E14 and develop draft text
June 2019-June 2019	Meet Face-to-Face at ICH Meeting to finalize scope of first stage Q&As
June 2019-June 2020	Refine text of first stage Q&As for S7B and E14
June 2020	Meet Face-to-Face at ICH Meeting to finalize first stage Q&As for S7B and E14
Jan. 2019-June 2020	Discuss potential second stage Q&As for E14 and generating any data needed
June 2020	Finalize timeline for second stage Q&A