**Final Concept Paper**
**ICH E14/S7B IWG Recommended Round 2 Q&As**

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## 1. Type of Harmonisation Action Proposed:

Second Round Q&A to E14 and S7B

## 2. Background to the proposal and statement of problem:

Q&As for ICH E14 and S7B were finalized recently (February 2022) and describe non-clinical and clinical integrated risk assessment strategies to inform the potential risk for proarrhythmia of a test substance. The Q&A connected these two related regulatory guidance documents to improve overall implementation and provided important clarifications. The E14/S7B Discussion Group (E14/S7B DG) now recommends developing a second round of Q&As to address any outstanding gaps before closing the topic.

Since 2000 and 2005 when ICH S7A and S7B were finalized, respectively, there have been updates to ICH M3 and S6; ICH S9 was also introduced. These guidance documents make recommendations for how safety pharmacology endpoints could be addressed. It is also likely that new ICH guidance, which may also address safety pharmacology endpoints, will emerge for modern drug modalities such as oligonucleotides. The recent ICH E14/S7B Q&As offer pathways to integrated risk assessment; they also describe best practice principles for key assays. Additional Q&As describe best practices for novel *in vitro* assays using human cardiomyocytes as well as the principles to be addressed in designing novel proarrhythmia models. The fundamental components of the proarrhythmia assessment are in place.

It is well known that small molecule drugs have higher off-target liability, including hERG potassium channel blockade. During drug discovery and development, the potential for a new small molecule to inhibit hERG channel function is a routine hazard identification test. ICH S7B suggests its scope is limited to small molecules presumably based on this observed ion channel liability. During the evolution of the ICH E14 guidance it was recognized that monoclonal antibodies and large targeted proteins represented a significant and important proportion of the drug development pipeline. These large proteinaceous molecules have a poor ability to cross plasma membranes and a very low probability of interacting directly with the hERG ion channel compared with small molecule drugs. Based on this low risk (and in the absence of a target-related change in cardiac repolarization), these modalities do not require a thorough QT/QTc study (ICH E14 Q6.3). However, Q6.3 doesn't specify definitions of large molecules and has been interpreted in a diverse fashion across regions. There were no Q&As for ICH S7B during the development of ICH E14 Q6.3 addressing these large molecules nonclinically. A large proportion of the modern drug development pipeline is now made up of novel modalities such as RNA-centric drugs (e.g., antisense oligonucleotides; small interference RNAs), antibody-drug conjugates, proteins, peptides, vaccines and gene therapies. Some of these new modalities have a more pronounced

separation of pharmacokinetic time course and pharmacodynamic effect. Overall, these new modalities change the balance of known and unknown effects, and on- and off-target effects. The resulting differences in specificity of target engagement change many elements of the drug safety testing paradigm.

The evolution of existing guidance and the introduction of new guidance, along with the evolving drug development pipeline exposes limitations in ICH S7B language and the ICH E14/S7B integrated risk strategies. In closing the ICH E14/S7B DG believes it would be timely and important to offer some additional clarity aimed at making the testing framework sustainable and flexible enough to limit potential regional differences in the recommended approach to this important safety endpoint for existing and emerging modalities.

## 3. Issues to be Resolved:

1. The current scope of ICH S7B is restricted to new chemical entities. Are nonclinical studies required to assess the proarrhythmia potential of biotechnology-derived agents?

   An assessment of the proarrhythmic potential is important and should be conducted for modalities beyond new chemical entities. The assessment should consider the on- and off-target effects of the molecules. The assessment may also need to be adapted to address the pharmacokinetic and pharmacodynamic profile of the test material. A statement of which modalities are in or out of scope could be provided. Ideally the directly safety pharmacology related guidance ICH S7A, S7B and S6 should all be consistent.

2. ICH S9, ICH S7A and ICH S6 all suggest safety pharmacology endpoints can be included in general toxicology studies. ICH M3(R2) encourages the incorporation of safety pharmacology endpoints in toxicology studies to the extent feasible to reduce animal use. What is necessary in order that toxicology study data can be used to inform an ICH E14/S7B integrated risk assessment?

   ICH M3(R2) encourages the incorporation of safety pharmacology endpoints into toxicology studies to the extent feasible. ICH M3(R2) Question and Answer 5(1) opines that technology is available to make safety pharmacology assessments in toxicology studies as rigorous as those in standalone cardiovascular safety pharmacology studies, provided that the methods have been adequately evaluated. The guidance suggests that, where toxicology data is to be used in place of standalone studies, the assessment should be as robust as in the standalone studies, but does not offer any advice concerning how this could be accomplished. Application of the best practice principles in the ICH S7B Q&As on heart rate correction, statistical sensitivity, positive controls, and exposure measurement to a large animal toxicology study could have the potential to make these studies comparable to parallel design standalone studies. Toxicology studies have the advantage of longitudinal assessment of effect which could be informative regarding the extended pharmacokinetics and/or pharmacodynamics of the test material.

3. Is there a framework like the integrated risk assessment described in ICH E14/S7B Q1 which can be used to inform what is necessary for QTc and proarrhythmia assessment of novel modalities?

   Novel modalities are often used to increase the specificity of engagement with the intended target. ICH S7A suggests that where there is increased specificity, and where off-target effects may be of lesser importance, not all safety pharmacology assessments are necessary. ICH E14 Q6.3 suggests that where mAbs and large-targeted proteins have a known mechanistic effect on repolarization the potential for cardiac repolarization delay should be assessed. In the absence of these on-target effects no dedicated clinical QTc assessment is necessary. These guidance documents already lay out a testing framework around two questions: are there known effects on cardiac repolarization and is there a potential for off-target effects on cardiac repolarization? The FDA has draft guidance on the clinical pharmacology assessment of peptides and oligonucleotides. Some modifications to the testing paradigm are already included. This suggests we may see more regional recommendations with the potential for inter-regional differences. It would be useful to take advantage of the existing ICH discussions.

   There is already language in the current ICH E14/S7B Q&As concerning confounding heart rate effects, as well as the potential for dose-limiting in vivo toleration issues confounding the ability to make an integrated risk assessment. A third question which could be included in the testing framework relates to the feasibility of an integrated risk assessment with the core battery of tests. Where core tests are not feasible the principles outlined in ICH E14/S7B Q2.2-2.5 and Q4.1-4.3 could be followed. There is an established precedent for follow-up studies already in ICH S7A and S7B. Ultimately, sponsors should provide a justification for modifications to the testing paradigm based on the outlined framework. Where there are significant modifications early engagement with regulatory authorities would be encouraged.

The IWG would also consider a review of the S7B, E14, and the combined E14/S7B materials to determine whether the organization of the content could be reorganized in a more logical manner designed to maximize clarity and understanding for readers.

The topics can be considered concurrently.

## 4. Planning

The DG recommends that its members, who have the appropriate nonclinical and clinical expertise, be reappointed to serve as members of the new implementation working group. It's anticipated that a new IWG, under the leadership of a new Rapporteur, could complete this focused activity within approximately 18 months.