Comments on S7B Step 2 Revision
The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarisation (QT Interval Prolongation) by Human Pharmaceuticals

1. Based on the current draft of ICH E14 and ICH S7B a thorough QT study will be required on all NCEs and that nonclinical studies are not required to support FIH studies. Given this situation there appears to be no regulatory value in nonclinical data since it is widely accepted that clinical data 'trumps' nonclinical. Thus the need for ICH S7B as a guidance document is not justified with the current draft of ICH E14.

2. The apparent inconsistency in the timing of CV nonclinical studies between ICH S7A and S7B is troubling and confusing.

ICH S7A states in Section 2.7.2 "The effects of the test substance on the cardiovascular system should be assessed appropriately. Blood pressure, heart rate and the electrocardiogram should be evaluated. In vivo, in vitro and/or ex vivo evaluations, including methods for depolarization and conductance abnormalities should also be considered."

Current industrial practice and state of the art CV science would suggest "appropriate evaluation of CV risk would include at a minimum both in vitro hERG and in vivo CV ECG data. However, ICH S7B states in Section 2.4 "Results from S7B ...generally do not need to be available prior to first administration in humans."

The impact of GLP also needs to be clarified/considered. If non-GLP hERG studies and in vivo telemetered studies are used for internal decision making prior to candidate nomination, these will have to be repeated because ICH S7A defines the need for GLP compliance and ICH S7B states the principles of ICHS 7A extend to it. Also, the preamble of the GLP regulations 21 CFR, 58.3 (d) clearly defines the need for all nonclinical safety supporting studies to be conducted to the GLP standard.

3. The regional differences in opinion about the utility of nonclinical data are very troubling and conflicts with the underlying principal harmonization. The consequence of this is that sponsor companies will be required to conduct extensive nonclinical studies for Europe and Japan and a thorough QT study for US.

4. Section 3.1.1 Use of Positive Control ... suggests the use of representative compound of the same class as a positive control. This unnecessarily repeats previously published work in animals and thus represents an inappropriate use of use of animals and conflicts with the generally accepted principles of animal use in research. This appears unnecessary if the sponsor can provide historical data to demonstrate that the selected study protocol has the desired sensitivity to detect the desired effect.

5. Line 15: Indicates that when QT interval is prolonged "there is" an increased risk for arrhythmia. This should read, "may be" since current data does not support the absolute increase in risk with QT prolongation of any magnitude and mechanism.

6. Line 47: Might better read "**Currently,** the most common **known** mechanism for QT interval prolongation from pharmaceuticals is inhibition of Ikr".

7. Line 76: The premise of the guidance is to define risk around QT prolongation. This line brings in models around pro-arrhythmia. Since this is currently a rapidly developing area and presently there are no well-accepted and highly predictive models in general use this should not necessarily be implied as a potential needed evaluation.

8. Line 83-85: Comment similar to comment for line 47.

9. Line 93-94: This is not a testing strategy, as it does not outline what needs to be defined and when and how to apply. It does represent a pragmatic risk assessment strategy.

10. Line 152: This would seem to imply that reference agents need to be incorporated in every assay. This definitely needs to be clarified. Is the expectation that validation and periodic studies reassessing "sensitivity" of the assay would suffice or is the intent to have a reference agent in every study??

11. Line 181-186: This is somewhat nebulous. Will this encourage the regulatory expectation of concurrent "positive controls" for all studies??

12. Line 214-217: There appears to be somewhat contradictory thoughts in these lines. States concentration ranges to above maximal estimated therapeutic exposure and then goes on to indicate that either establish a dose-response or reach physiochemical limitations. This should be clarified.

13. A number of pharmaceutical companies are investing in higher through put patch clamp technologies e.g. PatchXpress. These approaches provide exactly the same quality patch clamp data as the manual assay and therefore should be considered equivalent and therefore acceptable to ICH 7B. Lines 236 to 239 should not cover these technologies. This section should be rephrased to refer to the technology rather than the through put/capacity.