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Rockville, Maryland 20852

Ref: Docket No. 02D-0232. International Conference of Harmonization; Draft Guidance on S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals.

Abbott Laboratories commends the Agency on their efforts to provide guidance to industry and is very pleased to have the opportunity to comment on the "S7B Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals" ICH draft guidance, published in the Federal Register on June 14, 2002.

We thank the Agency for your consideration of our comments that are attached. Should you have any question, please contact Ivone Takenaka, PhD at 847-935-9011 or by FAX at 847-938-3106.

Sincerely,

Douglas L. Sporn
Vice President,
Corporate Regulatory Affairs

02D-0232

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**Comments on ICH – Draft Guidance on
S7B Safety Pharmacology Studies for Assessing the
Potential for Delayed Ventricular Repolarization
(QT Interval Prolongation) by Human Pharmaceuticals**

Docket No. 02D-0232

GENERAL COMMENTS

We commend the ICH Committees and Work Groups on the efforts to develop this guideline for industry. We find, indeed, this guideline to be very helpful as it addresses major issues on how to assess the potential risks of pharmaceuticals to humans during their preclinical evaluation. Thus, we strongly believe that the development of a related ICH Efficacy guideline addressing design of clinical trials, dose-effect relationships, recommendation of further tests for the evaluation of pharmaceuticals that delay ventricular repolarization or prolong QT intervals, the regulatory implications and risk management strategies would be extremely helpful for industry and would also harmonize the clinical evaluation requirements across the ICH regions.

Many examples of *in vitro* and *in vivo* methodologies that can be utilized to assess the potential for pharmaceuticals to delay ventricular repolarization or prolong the QT interval are provided in the guideline. However, the guideline does not provide guidance regarding the conduct of subsequent preclinical and clinical development activities when signals of delayed ventricular repolarization or prolonged QT intervals are observed. We request that such details be provided in the final guideline.

SPECIFIC COMMENTS

1. INTRODUCTION

1.1. Objectives of the Guideline

The guidance lists as one of the objectives, “2) the recommendation of study types and timing of studies in relation to clinical development.”

Comment:

We appreciate that in general preclinical studies are performed before clinical studies, however, the guidance does not address the timing of studies in relation to clinical development. We believe an algorithm or flowchart would be helpful to lay out when certain preclinical studies are needed, for instance, based on study outcome as explained in Section 2.3.2 (e.g. "If assessment of the pharmacological/chemical class yields a positive signal and there is a positive result in the *in vivo* assay, additional nonclinical testing is not necessary to support initial clinical studies.")

2. GUIDELINE

2.3.2. Further Considerations for the Nonclinical Testing Strategy

- **Item 4.** The guidance states that “In circumstances where clinical studies have not confirmed a signal of potential risk for QT prolongation observed in nonclinical studies, retrospective evaluation or follow-up nonclinical studies may be appropriate to understand the basis for the discrepancy (e.g. determination of metabolic differences or existence of large margins of safety)”.

Comment:

While the guidance does not mandate additional nonclinical studies in the above scenario, even the recommendation (“may be appropriate”) may be overly zealous. If a signal is detected preclinically, and rigorous clinical studies to evaluate effects on the QT interval do not confirm a signal, then the utility of additional nonclinical studies is not apparent. While it would be interesting to identify a reason for the discrepancy between the preclinical and clinical findings, in reality this discrepancy may not be explainable. As long as rigorous clinical evaluation of QT effects does not demonstrate a signal, then no additional preclinical testing should be required or recommended.

- **Item 5.** The guidance states, “If postmarketing or clinical study data suggest a potential QT interval prolongation effect despite negative findings in the available nonclinical studies, follow-up nonclinical studies to address this discrepancy can be valuable.”

Comment:

We recommend the guidance to provide more detailed recommendations on the types of follow-up studies would be appropriate to evaluate such discrepancies.

2.3.3. Implications of Nonclinical Studies

In the last paragraph of this section, the guidance states, “In the presence of a signal of potential risk, a purpose of *in vivo* QT assessments is to provide nonclinical data to estimate margins of safety and guide clinical study design. However, even large margins of safety based on nonclinical data are not considered to be a basis for dismissing a signal of potential risk”.

Comment:

The sentence “dismissing a signal of potential risk” needs clarification as to whether it refers to a clinical signal. Clearly, even in the event of no preclinical evidence of QT prolongation, it is still necessary to rigorously assess for QT

prolongation in clinical trials. However, if a preclinical signal is seen at large margins of safety, yet no signal is seen in clinical studies (including studies with metabolic inhibitors, renal or hepatic impairment, or any other scenario that might result in substantially elevated test drug plasma levels), then it would seem reasonable to "dismiss" the preclinical signal.

3. TEST SYSTEMS

3.1.3. In Vivo Electrophysiology Studies

The guideline states "The dose range evaluated in *in vivo* electrophysiology studies should include and exceed the anticipated human exposure when feasible".

Comment:

We request more specific information to be provided in the final guideline in regards to what the Agency considers to be the appropriate margin of exposure in animal models relative to the anticipated human dose.

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