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December 10, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Critique of Document No. 2004D-0378— International Conference on Harmonization, Draft Guidance on S7B: Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

To Whom It May Concern:

The members of the S7B Expert Working Group should be complemented on the Step 2 draft guideline. The guidance to industry is logically conceived and offers a degree of flexibility that allows us to tailor our specific strategy for assessing new drugs for risk of prolonging ventricular repolarization to the overall organizational drug development strategy, while assuring human safety.

General Comment

- Does the EWG intend that the guidelines will provide sufficient detail to inform the reader who lacks background on drug effects on ventricular repolarization and the assays associated with testing? If so, then there may not be sufficient detail in the draft 2 guideline for these individuals.
- The ICH S7A guidelines provide sufficient direction for in vivo testing of new drugs for effects on ventricular repolarization. Greater reference to the methodology in ICH S7A will allow the EWG to minimize redundancy between the two documents. This will also allow the EWG to focus the guidance to industry on those topics not addressed in ICH S7A; i.e. clarifying the need for corrected QT interval given the QT-RR relationship.

Specific Comments

Section 1.3 Scope of the Guideline

Line 54: Suggest alternative wording, "Pharmaceuticals for which testing is optional or can be excluded are described in ICH S7A."

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Section 1.4 General Principles

We agree with the exclusion of GLP requirements in ICH S7B, as reference to ICH S7A requirements for non-GLP studies assures appropriate documentation for study reconstruction. This level of flexibility provides the opportunity to introduce new emerging methodologies to the non-clinical study of potentially problematic drugs, recognizing the need for better predictors of drugs at risk of producing torsades de pointes.

Section 2.1 Objectives of S7B Studies

Guidelines should specify expectations for measurement of bath concentrations in in vitro assays for addressing the potential loss of compound.

Section 2.2 Considerations for Selection and Design of Studies

Line 86: Suggest alternative wording, "Experimental models that possess the full complement of molecular, biochemical, and physiological systems that can be more informative with regard to the clinical response to the test substance."

Section 2.3.3 Chemical/pharmacological class

While it is easy to see that certain chemical classes might be associated with an increased risk, there is no justification for considering pharmacological class as part of the risk assessment, unless it is suspected that the increased risk is mechanism based. In the case of one of the pharmacological class examples, the H-1 receptor antagonists, it is well known that members of this pharmacological class cover the spectrum from very high risk (astemizole) to no risk (fexofenadine).

Section 2.3.5 Follow-up studies

Line 130: Add bullet referring to the relevance of findings in the non-clinical assay to the identification of effects on ventricular repolarization in man.

Section 2.3.6 Integrated risk assessment

Line 147: Suggest alternative wording, "The integrated risk assessment should be scientifically based and appropriately tailored to describe the potential risk of adverse outcomes associated exposure of subjects or patients to the test substance."

Line 154: Assay sensitivity and specificity; Referring to the General Comment, will a reader understand what is meant by assuring/defining the assay sensitivity and specificity?

Line 155: Add "If applicable," before "Contribution of metabolites to QT interval prolongation as well as metabolic differences between humans and animals."

Section 2.3.7 Evidence of risk

Line 158: The integrated risk assessment needs to factor all the evidence of risk. More specifically, the final risk assessment needs to be characterized by the weight of evidence approach in regards to both the preclinical (in vitro and in vivo) and clinical data.

Section 2.4 Timing of S7B Nonclinical Studies and Integrated Risk Assessment in Relation to Clinical Development

The guidance should be more specific and definitive.

Line 163: "...generally do not need to be..."; suggest alternative wording, "...do not need to be...". Prior to first administration to humans, those studies required under S7A, including in vivo assessment of ECGs, will have been completed. In addition, Phase I trials will occur in a controlled setting, where ECGs will be carefully monitored to minimize the risk to the clinical subject/patient. Based on this fact, the word, "generally" can be removed from line 163 and the statement can be more definitive.

Section 3.1 Considerations for Test Systems

This section would benefit from references to the various statements for the readers who lack the background to this area of study. References appeared in the earlier versions of the guidelines.

Section 3.1.1 Use of positive control substances and reference compounds

Line 181-184: For each definition of a class there seem to be comparable numbers of compounds that do and do not increase the risk of Torsade de Pointes in humans, it could be meaningless to select reference compounds based on pharmacological class unless the mechanism is straight forward and clear.

Line 185: "Whether or not positive substances....should be justified." This statement appears as a mandate as would be found in a regulation. This is out of context with a

guidance document where recommendations are being proposed. We suggest deletion of this statement.

Section 3.1.2 In vitro electrophysiology studies

Line 197: "...triangulation..." is a new concept and study of its relevance to a risk of ventricular repolarization is currently in progress at a number of institutions. Suggestion: the guideline provides a definition of triangulation and clarification that the fact that this is a newly emerging methodology that may or may not ultimately be proven to be of value.

Line 202: typo: "the" for "he" expression.

Line 214: If there is a requirement for in vitro studies to test ascending concentrations until a concentration-response curve has been characterized or physicochemical effects become concentration-limiting, then the document should indicate how these data will be used in cases where the in vitro concentrations far exceed clinically achievable exposures. If the purpose is to establish a safety margin, the guidelines should define an upper limit of testing in vitro in the absence of activity, that is not dependent on limits of physico-chemical properties of the test substance or effects on the test system. For example, 100 fold or 300 fold the unbound concentration projected or directly measured for efficacy would be reasonable margins at which a test substance is reasonably free of adverse cardiac effects (effects on ventricular repolarization)

Line 223: suggest emerging data on the test substance be included which may influence the interpretation of the data when in vivo nonclinical or clinical studies reveal QT interval prolongation that is not corroborated by in vitro studies. For example, hERG traffic problem in addition to metabolites etc.

Line 226: actual concentration should be measured and reported instead of nominal concentration

Section 3.1.3 In vivo electrophysiology studies

Line 253: "...studies, regional information regarding..."; what is meant by regional? Does this refer to ventricular vs atrial, epicardial to endocardial changes, specific areas of the ventricle? should be more specific.

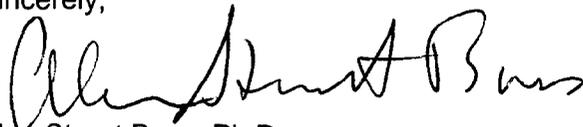
Line 264: The concept of QT-RR relationship has not been defined for the reader. Thus, "Therefore, the interpretation of data from..." will not be clearly understood unless the reader has background to the concerns related to determination of correct QT interval. Further recommendations in this section (ie. ...such as Bazett...) can also be misleading. The authors in an attempt for brevity have reduced this important section to

a point where the recommendations of the EWG are unclear. We would suggest that the authors definitively indicate that Bazett is not appropriate for use in animal studies based on a preponderance of data.

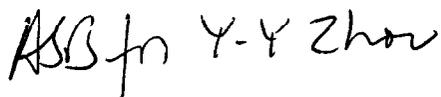
Section 3.1.4 Simulated pathological conditions and arrhythmias

Line 302: Suggest alternative wording, "...changes in action potential configuration might have utility in assessing the risk of proarrhythmia."

Sincerely,



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