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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, Maryland 20852

RE: Docket No. 02D-0232  
Draft Guidance ICH S7B,  
Safety Pharmacology Studies for Assessing the Potential for Delayed Ventricular  
Repolarization (QT Interval Prolongation) by Human Pharmaceuticals

Merck & Co., Inc., is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$3 billion annually on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market today.

Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations. MRL tests many compounds as potential drug candidates through comprehensive, state-of-the-art R & D programs. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

Since the inception of the International Conference on Harmonization (ICH), Merck has participated with health authorities from around the globe in the harmonization of regulatory standards. The objectives of ICH are to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that new therapies reach patients as swiftly as possible.

In the course of bringing Merck product candidates through developmental testing and clinical trials, Merck scientists regularly address issues affected by this proposed Guidance. Indeed, we have extensive experience in conducting safety pharmacology studies for new molecular entities intended for human use. In addition, Merck contributed to the drafting of this Guidance as a participant of the ICH Safety Expert Working Group. For these reasons, we are very interested in and well qualified to comment on this ICH proposed Guidance.

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We commend the Food and Drug Administration for seeking scientifically based harmonized technical procedures for pharmaceutical development through the ICH process. We have reviewed the document in detail and offer the comments below for consideration as this Guidance evolves. We organized our comments by section number to follow the content of the Guidance.

***Section 2.3.1, Recommended Nonclinical Testing Strategy***

***1. Evaluation of whether the test substance belongs to a pharmacological/chemical class known to prolong QT interval in humans (see below).***

Most particularly in Section 2.3.1, but also alluded to in other sections of the Guidance, is the recommendation to determine whether a test substance belongs to a pharmacological/chemical class known to prolong QT interval in humans. Under *Further description of figure*, it is suggested that any drug that prolongs QT interval in humans implicates all test substances in the same pharmacological/chemical class.

At the top of page 5, "Class can be defined by:

- Therapeutic group (e.g., antipsychotics),
- Mode of action (e.g., H-1 antihistamines, antiarrhythmics)
- Chemical structure (e.g. fluoroquinolones)."

The pharmacological/chemical class is not sufficiently defined to use as an independent criterion to designate a test substance as having a signal of potential risk. This inclusive approach is based upon judgment (e.g. a chemical subset of fluoroquinolone antibiotics versus all fluoroquinolone antibiotics versus all antibiotics) without a scientific basis.

This approach can be criticized as implying two levels of assessment, a higher standard for test substances that are pharmacologically/chemically related to previous offenders versus a lesser standard for novel structures. A first evaluation, particularly by therapeutic group, might introduce bias for an unreasonably high level of nonclinical assessment for a new agent in a suspect therapeutic class (e.g., antipsychotics) beyond that expected or necessary for a new agent. In addition, it is incorrect to suspect that a drug might prolong QT interval in humans merely based on the disease for which it is being developed.

Recommendations: In Section 2.3.1, as well as later sections where it is mentioned or implied, eliminate reference to "pharmacological/chemical class" as an independent criterion to indicate that a test substance signals potential QT risk. Alternatively, substitute "structurally/chemically similar" for "pharmacological/chemical class."

Delete the text in Section 2.3.2, Item 2, and replace it with the statement that follows so that it is consistent with ICH Guidance S7A, Safety Pharmacology Studies for Human Pharmaceuticals, Section 2.2, General Considerations:

“Consideration should be given to the test substances that belong to a structural/chemical class or group of pharmaceuticals of which many, though not necessarily all, members have been shown to induce QT interval prolongation in humans.”

*Section 2.3.1, Recommended Nonclinical Testing Strategy*

**2. Results from an ionic current assay that measures  $I_{Kr}$  or the current through an expressed  $I_{Kr}$  channel protein, such as that encoded by hERG (see sections 3.1.2 and 3.2.1).**

It is not clear what level of activity or potency in this assay should represent a concern for clinical safety. The concept of margin/therapeutic window for adverse effect on repolarization versus intended effect is not well represented in this Guidance, as evidenced by the third paragraph of Section 2.3.3. If activity at any concentration, without consideration to a safety margin, leads one to conclude a “signal of potential risk”, the majority of potential development candidates will fall into this category. However, it is well documented in the literature that many drugs without evidence of QT interval prolongation in humans are active in this assay at concentrations above their therapeutic concentrations (e.g. ciprofloxacin, fexofenadine, loratadine, risperidone, and verapamil).

Recommendations: In assessing the potential risk of a test substance to prolong QT interval in humans, the potency (concentration) of activity in  $I_{Kr}$  assays should be considered. This is consistent with *Section 2.1, Objective of Studies*, where it states, “2) relate the extent of delayed ventricular repolarization to the concentrations of the parent substance and its metabolites.”

- Remove the last bullet in Section 3.1.2, *In Vitro Electrophysiology Studies*, so that it becomes a concluding paragraph that reads:

“Results from in vitro assays have an important role in hazard identification but alone are not considered reliable for predicting safety margins. *However, the potency of activities in in vitro electrophysiology studies should be considered in the design of in vivo electrophysiology studies and in assessing the possible risk to humans.*”

- Delete the last sentence from the third paragraph of *Section 2.3.3, Implications of Nonclinical Studies*, ~~However, even large margins of safety based upon nonclinical data are not considered to be a basis for dismissing a signal of potential risk,~~ and replace it with the following text:

“As with the assessment of any potential adverse effect, appropriate consideration of therapeutic window, i.e. margins between intended “therapeutic” effect and unintended effect that may translate into an untoward effect on ventricular repolarization or QT interval, should be applied in the assessment of risk for a new test agent. Wherever feasible, analogous in vitro or in vivo test systems should be utilized to assess therapeutic window for intended effect versus untoward effect on ventricular repolarization or QT interval.”

***Section 2.3.1, Recommended Nonclinical Testing Strategy******3. Results from a ventricular repolarization assay that measures action potential parameters in isolated cardiac preparations (see sections 3.1.2 and 3.2.2) or specific electrophysiological parameters indicative of action potential duration in anesthetized animals (see sections 3.1.3 and 3.4.3).***

The role of *in vitro* repolarization assays as a screening tool is questionable since there are several test substances that prolong QT interval in humans but are negative in these assays (e.g. terfenadine, bepridil, disopyramide, propafenone, and thioridazine). While *in vitro* repolarization assays are useful to elucidate a mechanism of action, their high false positive rate makes them a poor choice as a screening tool. The use of animals to generate these data for all drug development candidates is not justified.

**Recommendations:** Remove ventricular repolarization assays from the recommended nonclinical testing strategy (Section 2.3.1) since a comprehensive *in vivo* assay is required. Add text to Section 3.2.2.2, *Action Potential Duration in Multicellular Preparations*, describing the valuable role these assays play in determining mechanism and suggesting the use of well-designed and validated *in vivo* studies to satisfy the intended role of the *in vitro* repolarization assays for detecting all ionic mechanisms for repolarization. Modify the first paragraph by adding to an existing sentence so that it reads:

*“Perfusion to inner tissue segments of the multicellular preparation can be limited for some test substances and therefore, these assays are more valuable for elucidating mechanism of action and not as a general screen for risk.”*

***2.3.2, Further Considerations for the Nonclinical Testing Strategy******1. While scientific rationale for the selection of test systems and study design should always be provided, it is especially important to provide detailed justification for the selection of the in vivo test system and study design used to assess the risk for QT interval prolongation.***

The wording of Item 1 suggests that it is more important to justify the *in vivo* versus the *in vitro* test system. All test systems should be adequately and appropriately justified. The wording of Item 1 could be seen as requiring a higher level of justification for *in vivo* test systems resulting in bias toward specific or preferred *in vivo* models.

**Recommendations:** Item 1 should be revised to read:

*“While It is important to provide the justification and scientific rationale for the selection of test systems and study design should always be provided, it is especially important to provide detailed include justification for the selection of the in vivo test system and study design used to assess the risk for QT interval prolongation.”*

### *Section 2.3.3, Implications of Nonclinical Studies*

The following statements in Section 2.3.3 intimate that human clinical data are the definitive information upon which a risk of QT interval prolongation should be based; however, this is not stated directly.

- “On the other hand, the absence of findings in nonclinical studies for QT interval prolongation is not considered to preclude a potential risk to humans.”, and
- “However, even large margins of safety based on nonclinical data are not considered to be a basis for dismissing a signal of potential risk.”

Recommendations: The Guidance should make clear that a rigorous clinical safety assessment is the definitive tool through which it can be determined if a nonclinical finding of delayed ventricular repolarization translates to humans. Therefore, we suggest that the following text be added to the end of Section 2.3.3:

*“Carefully designed clinical studies can assess whether the potential for delayed ventricular repolarization identified in nonclinical studies is relevant to humans. The clinical findings should be considered conclusive.”*

### *Section 3.4.3, Anesthetized Animal, Specialized Electrophysiology in Anesthetized Animals, Ventricular monophasic action potential (MAP) and Ventricular effective refractory period (ERP)*

The text presents the MAP and ERP techniques as interchangeable by stating, “either can be used for assessment of effects of repolarization.” However, determination of ERP is a highly quantitative technique and is the clinical standard for the assessment of effects on ventricular repolarization (Josephson ME, Seides SF. *Electrophysiologic Investigation: General Concepts. In Clinical Cardiac Electrophysiology. Techniques and Interpretations.* Lea and Febiger, Philadelphia, 1979, pp 23-60). The MAP is a less quantitative alternative. For these reasons, ERP and MAP are not interchangeable.

Recommendations: The text under the ERP header should be revised to indicate that the methods are not interchangeable by deleting the last sentence. The quantitative benefit of the ERP and its analogy to clinical assessment should be described.

## **CONCLUSION**

In summary, we suggest that the draft Guidance be revised as described below to address the following concerns:

- Pharmacological/chemical class is not adequately defined and is overly valued as an independent criterion to indicate that a test substance signals potential QT risk.

Suggested Revision: Eliminate “pharmacological/chemical class” as an independent criterion to indicate that a test substance signals a potential QT risk.

- The concept of margin/therapeutic window for adverse effect on repolarization versus intended effect is not described adequately. Without attention paid to potency (concentration) and results from other assays, the hERG assay will yield many false positive signals for risk of QT interval prolongation in humans.

Suggested Revision: A discussion of potency as a factor for estimating risk and planning clinical studies should be included in Section 3.2.1.

- In vitro repolarization assays are of questionable value as a screening tool due to their high false positive rate.

Suggested Revision: Remove ventricular repolarization assays from Section 2.3.1. Add text to Section 3.2.2.2 to describe their value in determining mechanism.

- The wording of Item 1 of Section 2.3.2 suggests that it is more important to justify the in vivo versus the in vitro test system.

Suggested Revision: Remove emphasis on in vivo systems. Add the justification and scientific rationale for selection of all tests systems to Section 2.3.2.

- The wording of Section 2.3.3 intimates that human clinical data are the definitive information upon which a risk of QT interval prolongation should be based; however, this is not stated directly.

Suggested Revision: Clarify that a rigorous clinical safety assessment is the definitive tool through which it can be determined if a nonclinical finding of delayed ventricular repolarization translates to humans.

- The text presents the MAP and ERP as interchangeable techniques in Section 3.4.3.

Suggested Revision: The text under ERP header in Section 3.4.3 should be revised to indicate that the methods are not interchangeable by deleting the last sentence. The quantitative benefit of the ERP and its analogy to clinical assessment should be described.

We welcome the opportunity to meet with you to discuss these issues.

Sincerely,



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