

**ABBOTT LABORATORIES**  
**Global Pharmaceutical Regulatory Affairs**

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December 13, 2004

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

Re: **Docket No. 2004D-0378, CDER 200494. International Conference on Harmonization; Draft Guidance on S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals**

Abbott Laboratories (Abbott) is very pleased to have the opportunity to comment on the above mentioned draft guidance published in the Federal Register on September 13, 2004.

We thank the Agency for their consideration of our attached comments. Should you have any question, please contact Ivone Takenaka, Ph.D. at (301) 998-6144 or by FAX at 301-984-9543.

*Sincerely,*

  
Douglas L. Sporn

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**Comments on ICH Draft Guidance on  
S7B Nonclinical Evaluation of the Potential for  
Delayed Ventricular Repolarization (QT Interval Prolongation) by  
Human Pharmaceuticals**

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The following comments on the above-mentioned Draft Guidance are provided on behalf of Abbott Laboratories.

**COMMENTS**

**2.0 GUIDELINE**

**2.1 Objectives of S7B Studies**

**Lines 65-66** – The document cites one of the objectives of S7B studies as “...to... 2) *relate the extent of delayed ventricular repolarization to the concentrations of a test substance and its metabolites.*”

**Comment**

Two specific issues need clarification in the guidance.

1. “*Concentrations of a test substance and metabolites*”. It is clear that targeted concentrations in test chambers are not always achieved when drugs are added to *in vitro* test systems. Thus, one needs to verify the concentration (exposure) achieved in the test chamber to reliably relate the extent of the effect to the test substance (or reference) concentration (Sec 3.1.1).
2. The nature and concentration of metabolite(s) in man are unknown prior to early clinical studies. Thus, it is unreasonable to expect that metabolites will be tested *in vitro* prior to such studies. In contrast, if *in vivo* preclinical QT findings (QT prolongation) are qualitatively different from *in vitro* findings with the parent compound (e.g., QT prolongation but no hERG block), the electrophysiologic effects of metabolites should be evaluated.

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

**Lines 162-164** – The guidance states “*results from S7B studies assessing the risk for delayed ventricular repolarization and QT interval prolongation generally do not need to be available prior to first administration in humans.*”

**Comment**

Is it not appropriate to expect that results from S7B nonclinical studies be available prior to first administration in humans to provide important safety

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guidance in regards to subject care and monitoring? Why would such information “not need to be available” prior to first in man studies (as stated in the document)?

### **3.0 TEST SYSTEMS**

#### **3.1.1. Use of positive control substances and reference compounds**

**Lines 177-180** - The document states, “*Positive control substances should be used to establish the sensitivity of in vitro preparations for ion channel and action potential duration assays. In the case of in vivo studies, positive control substances should be used to validate and define the sensitivity of the test system, but need not be included in every experiment.*”

##### **Comment**

Please clarify whether “*need not be included in every experiment*” also applies for *in vitro* preparations.

#### **3.1.2 In vitro electrophysiology studies**

**Lines 215-217** - The document calls for testing “*ascending concentrations ... until a concentration-response curve has been characterized or physicochemical effects become concentration-limiting*”.

##### **Comment**

If earlier studies demonstrate no hERG block at excessive multiples of C<sub>max</sub> (e.g., greater than 100-fold the predicted C<sub>max</sub> concentration), there is no need to further evaluate the effects of the compound at higher concentrations. Indeed, it is possible that non-specific effects on the test preparation may occur (depolarization, cell death) at these high relative concentrations that would confound interpretation of drug effects on hERG current. In addition, solubility studies in the buffer systems used would need to be performed to verify that the drug remained in solution at high concentrations in order to reliably characterize concentration-response relationships. Both limitations could confound the interpretation of hERG study results.

In addition, no mention is made of the need to consider the free fraction of test substances when determining *in vitro* target concentrations. Concentration-response curves (and hence sensitivity) *in vitro* can be prominently affected by drugs demonstrating significant plasma protein binding. Please clarify how this should guide the evaluation of test (and reference) compounds.

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### 3.1.3. *In vivo* electrophysiology studies

**Line 258-272** - This section discusses the confounding effects of heart rate on the evaluation of drug-induced changes of cardiac repolarization and corrected QT (QTc) values in intact animals.

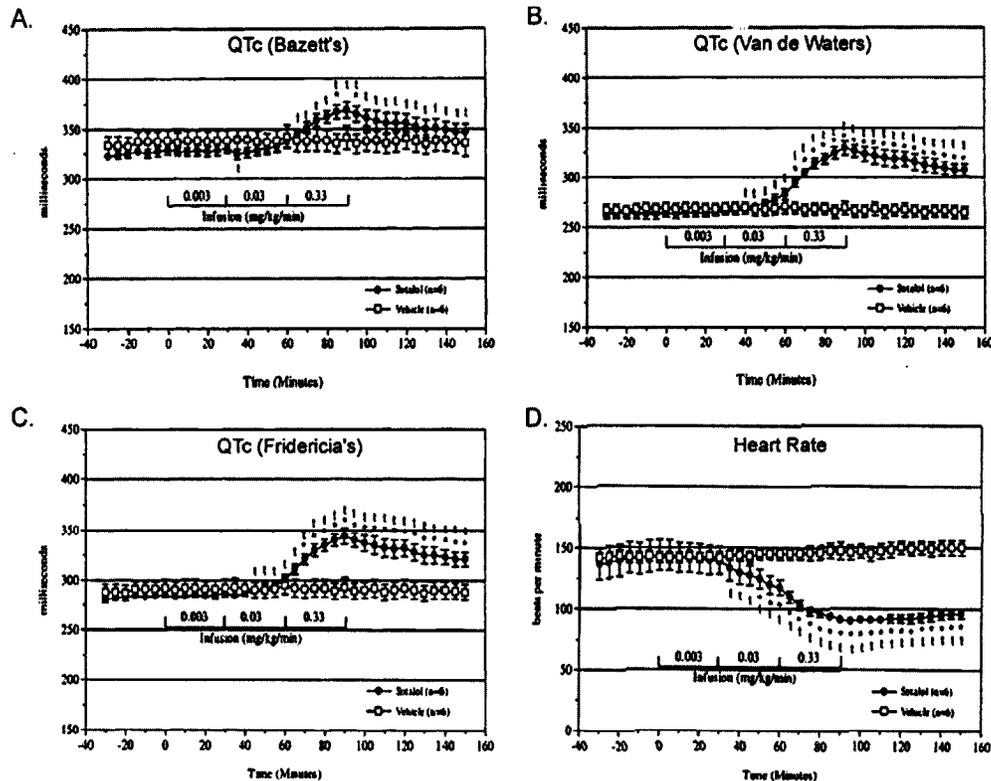
#### Comment

One commonly used species for *in vivo* electrophysiologic studies is the dog. However, sinus arrhythmia is prominent in the conscious dog, as are wide swings in heart rate accompanying activity and excitement. Such heart rate variability may lead to greater variability in derived QTc values. In contrast, sinus arrhythmia and changes in autonomic tone due to activity and excitement are absent in the pentobarbital-anesthetized dog, another model widely used in preclinical safety studies. We routinely use the instrumented, closed-chest anesthetized dog model for the preclinical assessment of hemodynamic as well as electrophysiologic effects of novel compounds. This model not only minimizes beat-to-beat variability of heart rate, but also affords well-controlled exposure using i.v. infusions and frequent measurements of plasma concentrations. This model also minimizes untoward neurological and gastrointestinal adverse effects of supratherapeutic drug concentrations, such as nausea and vomiting, and variability of absorption via oral administration. Consequently, pharmacokinetic data derived from this model is robust and reproducible. We have found this model invaluable in evaluating effects of drug candidates on cardiac repolarization.

Figure 1 (below) illustrates the effects of sotalol and vehicle (Dextrose, 5% USP) in the pentobarbital-anesthetized dog model on the QT interval corrected by either Bazett's, Van de Water's, or Fridericia's formula and heart rate. Note the consistency of heart rate and QTc values for the vehicle group. With increasing plasma concentrations of sotalol, QTc values increase for all three correction factors. The threshold for statistically significant drug-induced increases in QTc values obtained with Van de Waters and Fridericia's correction factors are essentially equal, occurring during the middle of the second infusion period. In contrast, Bazett's correction factor proved to be less sensitive in detecting prolongation of the QTc interval, with consistent significant differences obtained during the third infusion period. The partial reversibility of changes in QTc values is also demonstrated by their decline during drug washout period. Thus, the present data demonstrates that the anesthetized canine is a clinically-relevant and sensitive model for the characterization of hemodynamic and electrocardiographic effects of drug candidates.

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## Effect of Sotalol or Vehicle on the Corrected QT Interval in the Anesthetized Dog



**Figure 1.** Effects of increasing sotalol concentrations on the corrected QT interval and heart rate in the pentobarbital-anesthetized dog model. Panels illustrate the QT interval corrected by Bazett's (A), Van de Waters (B), and Fridericia's (C) correction factors; Panel D depicts the changes in heart rate. Asterisks indicates  $p < 0.05$  in treated animals vs. vehicle, while "t" indicates  $p < 0.05$  change from baseline, treated animals vs. vehicle. Sotalol was infused at rates of 0.003, 0.03 and 0.33 mg/kg/min for 30 minute periods; concentrations measured at the end of each i.v. infusion period were  $0.17 \pm 0.06$ ,  $1.18 \pm 0.16$ , and  $14.48 \pm 1.21$   $\mu\text{g/mL}$  (mean  $\pm$  SEM,  $n=6$ ). (R&D/04/479)

**Lines 273-276** – The guidance states “[L]aboratory animals used for in vivo electrophysiology studies include dog, monkey, swine, rabbit, ferret, and guinea pig”.

### Comment

With such rapid basal heart rates, the smaller mammals mentioned may not be considered appropriate for key critical QT studies, similar to adult rats and mice, which are recognized by the guidance (line 276) as not being appropriate species for such studies.

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### **Additional Comments**

1. Further emphasis needs to be placed on demonstrating the sensitivity, reproducibility, and reliability of the methods of analysis (QT detection software) for the *in vivo* studies. Assay sensitivity limits need to be established and maintained. If the guidance recommendations are to rely primarily on only two assays (namely *in vitro* hERG and *in vivo* QT), and the hERG assay has been shown to detect “false positive” compounds (fluoxetine, verapamil), it is essential to have in place a robust preclinical QT assay (reliable in both methodology and critical evaluation). Indeed, it is unfortunate that the APD assay, which measures an integrated *in vitro* response and provides a “check” on the more complex QT *in vivo* assay results, has been relegated to an ancillary function.
2. No mention is made on changes in the configuration of the T wave in preclinical studies, or how such changes should be further evaluated.