

December 13, 2004



GlaxoSmithKline

Management Dockets, N/A
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**Re: NAS 0; Not Product Specific
General Correspondence: Other
Comments on Draft Guidance for Industry: The Nonclinical Evaluation of the
Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by
Human Pharmaceuticals [Docket No 2004D-0378]**

Dear Sir or Madam:

Please find enclosed comments from GlaxoSmithKline on the Step 2 (revised 10 June 2004) draft of the ICH S7B Guidance for Industry: The Nonclinical Evaluation of the Potential for Delayed Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. We appreciate the opportunity to provide comments on this draft guideline. Our main concern at this time is the lack of a clear relationship between ICH topics E14 and S7B, particularly given the reference in the current draft E14 to continuing regional differences in the role of nonclinical data in QT assessment (please see our comments to Docket 2004D-0377 submitted November 12, 2004). We have relatively few comments on the current draft S7B and are in general agreement with the content. Specific comments are provided on subsequent pages.

This submission is provided in paper and in electronic format according to the instructions provided at
<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm?AGENCY=FDA>

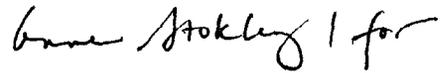
2004D-0378

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Please contact me at (919) 483 4483 if you require clarification of any of these comments.
Thank you for your consideration.

Sincerely,

A handwritten signature in black ink, appearing to read "Alison Bowers" followed by a flourish.

Alison Bowers
Director, Policy, Intelligence, Education
Regulatory Affairs

Cc: Douglas Throckmorton, M.D.
John Koerner, Ph.D.

Comments on S7B

Timing of studies (Section 2.4)

The recommendation for the nonclinical studies to be carried out early is useful.

Nomenclature of K channels

The latest K channel nomenclature for hERG and KvLQT1 channels is KCNH2 and KCNQ1, respectively. Whilst hERG is still the preferred/most widely used name for the former channel, KvLQT1 is now more frequently referred to as KCNQ1 in the literature so the guideline should be updated to use this name.

Use of positive controls and reference compounds (Section 3.1.1)

It is suggested that while positive controls should be used in *in vitro* and *in vivo* studies, they are not necessary in every *in vivo* study. Why is this distinction made?

In vitro electrophysiology studies (Section 3.1.2)

This section mentions measuring APD30 to obtain information on Phase 2 of the action potential and triangulation. In dog PF preparations (and possibly other preparations) this is not the best measure during the plateau; APD40 is more appropriate. The Guideline should be modified to “APD30 or APD40”. There is some literature data to support this.

Testing metabolites (Section 3.1.2) (should this be 3.1.3 line 282?)

This section could be read as requiring that, in the event of a discrepancy between *in vivo* and *in vitro* data, all metabolites be tested in an *in vitro* system. Assuming this is not what is meant, clarification is needed. Maybe “metabolites” could be changed to “major metabolites”.