



Medical Products Group

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

RE: *Guidance for the Use of Bayesian Statistics in Medical Device
Clinical Trials; Draft Guidance for Industry and FDA Staff
[Docket 2006D-0191]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," published in the Federal Register on May 23, 2006 at 71 FR 29651.

Thank you for the opportunity to provide these comments. We are encouraged by FDA's willingness to assist sponsors in the use of the Bayesian approach and view issuance of this guidance document as a positive development.

General Comments

Pre-submission meetings

As early and frequent communication between FDA and the sponsor is an important element in ensuring the successful application of the Bayesian statistical approach, we recommend FDA create within the guidance document a section on pre-submission meetings. Pre-submission meetings are encouraged in several places in the document. For example:

Page 6 (lines 156-161)
Page 8 (lines 254-255)
Page 9 (lines 266-267)
Page 17 (lines 592-595).

For ease of use and assistance in sponsor planning, we recommend consolidating this information into one section. In this section we recommend FDA provide additional

2006D-0191

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guidance to sponsors to assist in determining whether pre-IDE or agreement meetings are more appropriate for these discussions. Both meeting types are mentioned in the document. We recommend including, in this section, topics for discussion at the pre-submission meetings, such as the determination of modeling choices, identification of scientifically valid prior information, use of prior information in the analysis, mathematical model, data presentation in product labeling, and other necessary components to assist in a successful outcome.

Prior Information

It is stated that, "good prior information can have greater impact on the analysis of the trial and thus on the FDA decision process" (page 5). Additional guidance as to what constitutes good prior information would be useful. The text discussing prior information on pages 16-18 and later on page 30 appears to contain some inconsistencies, especially in regards to expert opinion.

In vitro diagnostic devices (IVDs)

The document provides examples of the application of Bayesian statistics to non-IVD medical devices. We recommend providing examples of the application of Bayesian statistics to IVDs. Alternatively, we recommend the inclusion of references on this topic, such as Jan Krouwer's book "Assay Development and Evaluation - A Manufacturer's Perspective," which describes the use of prior knowledge in IVDs.

Specific Comments

1. Page 9, Line 275

Insert the word "predictive" after "perform simulations to assess" to avoid confusion with the frequentist approach.

2. Page 9, Line 283

Include factors to consider in justifying choices of prior information.

3. Page 9, Lines 286-289

Provide additional guidance as to the expression of clinical data in labeling so they are "easy to understand." We also recommend including clinical data expression in labeling as a pre-submission meeting topic.

4. Page 15, Line 533

Since covariate adjustment is complex within the Bayesian paradigm, provide additional guidance regarding covariate adjustments, including references specific to Bayesian techniques.

5. Page 17, Line 607

Correct typographical error by deleting "or" after "clinical evaluators."

6. Page 22, Line 820



Provide additional guidance on the application of Bayesian approaches to clinical trials with co-primary endpoints. It does not appear that both co-primary endpoints would have to be designed and analyzed with the Bayesian approach. However, clarification would be useful.

7. Page 25, Line 928

Address multiple looks and penalties using the Bayesian approach. It is well understood that penalties in terms of type I error rate are applied to interim analyses and multiple looks of the data using the frequentist approach. However, adjustments to control type I error for interim analyses seems contrary to the Bayesian approach of updating a prior.

8. Page 35, Line 1299

Clarify "(2) you iteratively increase the variance of the prior distribution by trial and error until the type I error rate reduces sufficiently." It is unclear whether this statement applies to calculations of actual posterior probability or simulation only.

Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-3106. For questions pertaining to technical aspects of these comments, please feel free to contact Roseann White, Acting Director Clinical Science, Cardiac Therapies at (408) 845-1498.

Sincerely,

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Abbott Laboratories