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June 1, 2010

To: Division of Dockets Management
Re: Docket # FDA-2010-D-0090

The International Society for CNS Clinical Trials and Methodology (ISCTM) commends the FDA for preparing a draft of the comprehensive Guidance for Industry, "Adaptive Design Clinical Trials for Drugs and Biologics". This timely document presents valuable standards by which Adaptive Design trials can be planned, implemented and interpreted.

Recognizing the importance of this document for our constituency, the ISCTM convened a working group to review and comment on the guidance.

Workgroup members included:

Chair: Andrew C. Leon PhD, *Weill Cornell Medical College*
Brendon Binneman MBChB, MRCPsych, *Pfizer, Inc*
Vlad Dragalin PhD, *Quintiles, Inc*
Judith Dunn PhD, *Roche, Inc*
Douglas Feltner MD, *Pfizer, Inc.*
Ilise Lombardo MD, *Pfizer, Inc*
Virginia Sutton PhD, *i3 Global*
Ibrahim Turkoz MS, *Janssen Pharmaceutica, Inc*

Specific Comments:

1. Line 23: Replace "include in the adaptive design" with "include in supportive documentation for the adaptive design"
2. Line 39: Add after "if one exists," the following "more accurate (e.g., higher precision)"
3. Line 99: Replace "analytic" with "analysis". This should be done throughout the document: the correct term is "Statistical Analysis Plan"
4. Lines 167-178: The term "bias" is used loosely: statistical bias (of an estimator, of Type I error rate), operational bias. We typically think of bias of an estimator. Another term might be used for Type 1 error and for operational bias.

5. Lines 187-188: Suggest "efficacy" replace "effectiveness" as effectiveness is more commonly associated with practical trials, pragmatic trials, simple trials, Phase IV trials, etc. (For example, see <http://www.ahrq.gov/downloads/pub/evidence/pdf/efftrials/efftrials.pdf>)
6. Lines 217-229: Clarify the FDA position on "operationally seamless Phase 2/3 design"
7. Lines 276-281: It is noted that a potential benefit of adaptive designs is increased efficiency regarding time to completion. This potential benefit is then balanced by the caveat that such benefit might come at the cost of study quality. This might make the use of adaptive design in clinical trials appear self-serving to readers of this document instead of noting some of the theoretical scientific advantages detailed later on in the document. It might be more in keeping with the intent of this document to be a bit more balanced up front, and to note additional potential benefits and intent of adaptive designs in advancing the science of drug development, while not minimizing the concerns of Type I errors. As noted in subsequent sections, there are important advantages to adaptive designs that should be at least alluded to up front to keep the general document more neutral.
8. Lines 415-417: Guidance is not supportive of seamless Phase II/III due to the careful thought that occurs and knowledge gained with separating the phases. It fails to note the potential benefit of restricting subsequent research (including a 2nd confirmatory trial) to appropriate patient subgroups, doses, etc. in terms of patient safety and public health. In general, guidance would be enhanced with more discussion of seamless phase II/III.
9. Lines 427-430: Statement is not clear. Please clarify. In fact both traditional and Adaptive design methods make assumptions, because there is limited knowledge available.
10. Lines 468-472: Section describes the benefits of adaptive design but is included in a section labeled Counterproductive Impacts of Adaptive Design. This paragraph might better fit earlier in the guidance than in section B.
11. Lines 1299-1301: The planning and results of simulation studies in general do not belong in either the protocol or the SAP. Suggestion: Create a separate document called Simulation Report to include the relevant information about simulation studies.
12. Line 1310: One can also simulate the possibly multiple ways to stop a trial for futility (impact on Type I and II error rates, etc.).
13. Lines 1313-1322: The first time, of only a few times, "modeling and simulation" is used here. This could be interpreted as Bayesian methods only being useful when modeling and simulation is used - Bayesian methods have broader usage in adaptive designs, not limited to planning and predictive probabilities, either. Suggestion: The following point

needs to be made clearly- Bayesian approaches can be useful with adaptive designs in general, from planning to execution, and that a variety of methods can be used in this context, including, but not limited to modeling and predictive probabilities

14. Lines 1341-1342: It would be useful to clarify conditions under which simulation-based Type I error rate control justification would/would not be acceptable.
15. Recommend inserting the following edits as highlighted:
 - a. Line 1408: inappropriate. The efficiencies of such a design are optimized when the time to the observed event is relatively short.
 - b. Line 1413: include edit as follows..... "efficiency (e.g. study size and time to observations of interest)...."
 - c. Line 1448 include edit as follows....."patients, independent unblinded data safety monitoring board oversight, until....."
 - d. Line 1458 include edit as follows....."then be necessary to carry out further safety studies or amend ongoing A&WC studies, leading in the end to....."
16. (Section 9): Adding "and Supportive Materials" to the title of this section CONTENT OF AN ADAPTIVE DESIGN PROTOCOL" would be helpful.
17. Lines 1462-1575: The planning and results of simulation studies in general do not belong in either the protocol or the SAP. Suggestion: Create a separate document called Simulation Report to include the relevant information about simulation studies. The timing of the preparation of the 'simulation report' needs to be clarified.
18. Line 1485: Please give more detail on what is meant by *supportive information*.
19. Lines 1518-1520: Please clarify when it is appropriate to calculate conditional power as opposed to using simulations for this purpose.