ISCTM
THE INTERNATIONAL SOCIETY FOR CNS CLINICAL TRIALS AND METHODOLOGY

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May 27, 2010

To: Division of Dockets Management
Re: Docket No. FDA-2010-D-0075

The International Society for CNS Clinical Trials and Methodology (ISCTM) commends the FDA for preparing a draft of the comprehensive Guidance for Industry, "Non-Inferiority Clinical Trials". It is a critically important document for non-inferiority trial design, analysis, and interpretation. It is unique in its perspective and attention to detail on this topic. The document presents valuable standards by which trialists will plan and interpret non-inferiority trials.

Recognizing the importance of this document, 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*
Atul Mahableshwarkar MD, *Takeda*
Joanne Severe MS, *NIMH*
Murray Stein MD, MPH, FRCPC, *University of California, San Diego*
Jane Tiller MBChB, FRCPsych, MBA, *Cephalon, Inc*

Below please find the feedback resulting from this working group:

General Comments:

1) The Figures, Commonly Asked Questions (sec V) and Examples (sec Appendix) were very helpful.

2) In light of the new push for comparative effectiveness trials, we have the following suggestion. The document could include specific reference to application of the non-inferiority design when comparing two FDA approved medications (each of which has previously been shown to have efficacy). Perhaps this could be included in the FAQ section.

3) The term “effectiveness” is used throughout the document however NIH and other PHS agencies typically distinguish between “effectiveness” and “efficacy”. Using the NIH nomenclature, it seems that “efficacy” would be a more appropriate term throughout the document.

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Specific Comments:

1) After line 135: Suggest include additional text to interpret 'Null' and 'Alt' hypotheses since they are opposite of how one thinks about them in superiority trials. Ex: Null=Test and Control too different to say Test is as good as Control; Alt=Test and Control close enough to say Test is as good as Control

2) Lines 246-249: Further clarification regarding the choice of active comparator would be helpful when there are a number of approved drugs in the class being studied. Thus, if there are a number of drugs in a class, should M1 be some measure of a mean effect size for the class regardless of the actual choice of the active comparator

3) The very long sentence that comprises lines 258-262 gets very confusing in the middle of line 261. Might be better to break it up and make it clearer.

4) In the paragraph about M2 that begins on line 304, an example of an M2 and how it relates to M1 would be very help here. There is such an example on page 17, but having another one earlier would be very helpful. Ex: If M1=10 and M2=4, this would mean that M2 preserves at least 60% of the effect of M1.

5) Line 433 and Line 704 – See line 300. Should line 433 be "null" or "alt"?

6) Lines 439-453 are very important as they emphasize that study implementation in a NI trial is critical. How does the FDA assess quality? Is there a requirement for study implementation metrics to before reviewing the results in a NI trial?

7) Line 539 – The word "modest" is vague and can take on different meanings.

8) Not sure which lines the following comment specifically relates to: should the basis for the choice of M2 be required, since it seems very subjective. In other words, should the choice of M2 margin itself be the subject of review?

9) Since M2 is some fraction of M1, does FDA plan to include in labeling of a new drug the M2 percentage, e.g., Will the label state: "This drug has been shown to be at least XX% as effective as drugabc"?

10) Line 692 – Change "on" to "of"

11) In section "Statistical Methods for NI Analysis" Lines 1100-1301 ----the section largely deals with difference between 'fixed margin' and 'synthesis' approaches. As described, both approaches rely heavily on historical data (in fixed margin, to set M1; in synthesis, is an estimate of control effect from meta-analysis of historical trials and is combined with actual NI trial data). Thus, it appears that the main difference between the two approaches (fixed margin vs synthesis) is in the computation of the variance, which may result in different efficiencies. But, it seems that the same potential biases of use of historical would be present in both approaches. I think it would be useful to discuss the similarities of the two approaches first, then the differences.

It might make it clearer that much of the exact same background and historical information are used in both approaches, and that how one goes about do the statistical tests is what is different.

12) Line 1300-1301 --- “on a less extreme bound of the confidence interval” – it might be clearer to say “a wider confidence interval” or a “more relaxed confidence interval”.

13) Section IV D: (1303-1330)Some discussion about considerations for establishing M2 when designing trials for safety/tolerability as opposed to efficacy would be beneficial. Similarly some guidance on selecting M2 in trials where both an active comparator and a placebo group are included would be helpful to the field.

14) General comment about M2: M2 is described as the loss of effect to be ruled out. In some ways this is like a double-negative. It gets confusing in some examples. The example on lines 1327-1330 is very confusing. It is difficult to comprehend if the 48% loss stated on line 1329 is correct or if it should be 52%. One way to help clarify the M2 might be to show the relationship of M2 to retention of effect. Ex: the smaller the choice of M2, the larger the effect of M1 that would be retained; the larger the choice of M2, the smaller the effect of M1 that would be retained.

15) Lines 1339-1341 discuss the importance of variance of the treatment effects and correctly point out that variance will not be known. Guidance about methods to estimate such variances would be helpful to determine the sample size for NI studies.