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May 27, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: FDA–2010–D–0075: Draft Guidance on Non-Inferiority Clinical Trials

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the draft guidance on *Non-Inferiority Clinical Trials*.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS

We note that the guidance appears to advocate the use of two margins, M1 and M2, and the use of a fixed margin method for M1 and the synthesis method for M2. Early in the document, however, more traditional approaches, such as applying a fixed margin method to M2, are discussed. Presumably these are being introduced to provide historical context, but BIO proposes that the guidance make it more clear which methods are being proposed, as early as possible and consistently throughout the document.

BIO proposes that the use of a single margin be considered for cases in which this could be equal to M1 and in other cases could be equal to M2. This would simplify the guidance considerably without appreciable loss of flexibility in dealing with each new situation in an appropriate way.

We also ask that the document provide additional guidance for the situation where the study has both an active control and a placebo control. For example, will different margins apply for the comparison to active control if such a comparison is desired for the label?

Because M1 has been introduced as the point estimate of the effect of active control relative to that of placebo and also as the limit of a confidence interval for that effect, this causes confusion regarding the value of M2, which is defined as a fraction of M1. The exact definition of M2 needs to be clarified. (In particular, see the reference to line 1798 in the detailed comments below.)

The guidance seems to make the assumption that the use of non-inferiority (NI) study is to establish effectiveness. This raises the question of whether M2 is an optional margin to be used only when the sponsor seeks special label language, or when the effectiveness of the test drug has been established, and the sole purpose of the NI study is to demonstrate "equivalence" to the active control.

BIO also proposes additional guidance for the case where the active control in a NI study was itself approved based only on active controlled studies using a previously-approved drug as control, such that no placebo-controlled historical data are available. For example, in such a case will it be appropriate to utilize the previously-approved active control's historical placebo-controlled data to determine a margin?

Please see the table below for detailed comments.

***Priority: 1= High, 2= Medium, 3= Low**

SPECIFIC COMMENTS ON TEXT **GUIDELINE SECTION TITLE: III. GENERAL CONSIDERATION OF NON-INFERIORITY STUDIES: REGULATORY, STUDY DESIGN, SCIENTIFIC, AND STATISTICAL ISSUES**			
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**	**Priority**
69-72	This sentence is helpful, as it is often assumed that NI trials are being done to explicitly compare to active control rather than to implicitly compare to placebo. This should be considered for inclusion in a summary section that emphasizes key points.	Please create a summary section that emphasizes key points in the Guidance, and include this point in that section.	3
87-88	It would be helpful to discuss whether assay sensitivity could be enhanced by including a (possibly	Please modify subsection A to include a discussion of whether inclusion of a small placebo group	2

	very small) placebo group.	would enhance assay sensitivity.	
94-99	It should be reinforced that a sample size calculation by itself is not sufficient to assess the ability of the study to have detected a difference.	Just before subsection 2, please add text that reinforces the idea that a sample size calculation alone is insufficient to assess the ability of the study to have detected a treatment between the test and control agents.	2
101	This section begins with superiority trials and then discusses noninferiority trials later.	Please add "...vs. that of the superiority trial" to the title of this section.	3
103-108	An assumption here is that larger values indicate superior treatment effects.	Please modify the Guidance to state the convention that larger values indicate superior treatment effects, either in this section or in earlier in the document.	3
123	The remark in parentheses regarding the study possibly being too small is speculative.	Please revise this sentence to read, “Point estimate of effect is 2; 95% CI lower bound is <0.”	3
130	Make explicit the use of confidence intervals rather than the simple "is thought to be", which may suggest a simple point estimate. Also, make it clearer that M1 is estimated from historical studies and is assumed to apply to the NI study.	Please revise this line to read "... where M1 represents the smallest value that, at a high confidence level, is thought to be the whole effect of the active control C, relative to placebo, and that would be expected to apply to the NI study".	2
135	Rather than introducing the key concept of M1 vs. M2 in a footnote, it would be better to introduce this early in the document in its own section.	Please introduce the concept of M1 vs. M2 in separate section, early in the document, rather than in a footnote.	1
143	Given the importance of this figure, adding all scenarios that can occur would be helpful.	Please modify the figure to include a scenario identical to #6, but with the lower confidence bound being less than zero.	2
143-161	Given that Figure 3 later in the document shows the role of both M1 and M2, it is unclear that Figure 2 and its subsequent points 1-6 are helpful. It may be best to proceed more quickly to the discussion of	Please delete figure 2.	2

	Figure 3.		
160-161	The outcome described may not be so rare if sample sizes are large. Is it clear that it presents interpretative problems, given that the pre-specified standards have been met?	Please delete the phrase regarding interpretive problems.	3
175		From this point forward, please replace “non-inferiority” with “NI” for consistency.	3
175-176		If there are contrary points of view regarding the ethics of a NI study vs. those of a placebo study, then those should be raised in this section. Please include FDA response to those views as well.	2
235-236	If based on p-values alone, this statement is not necessarily true, as there may be situations where the results are very similar but one comparison is significant and the other is not.	Please use a different example to make the guidance's point.	2
253	Make the Guidance clearer regarding the distinction between inferences made based on point estimates vs. those made on confidence intervals.	Please reword to "...would not in fact have been shown, with high confidence, to have any..."	3
266-268		Please clarify the meaning of “distribution of estimates” in this context.	3
286-287	This point is sufficiently important that it should also be highlighted in the discussion of Figure 3.	Please highlight in the discussion of Figure 3.	2
301-302	The spirit of this sentence is clear; i.e., that the NI study must be well-conducted and have assay sensitivity. However, this sentence, when taken literally, indicates that M1 is not known until the results of the NI trial are available. It is understood that the results for the active control in the NI study may raise questions regarding the study's validity. However, it should be	Please revise this sentence to read, “...the validity of the choice of M1 cannot be confirmed until the NI study is complete."	1

	clarified that M1 is not formally subject to change, as it is a design parameter for the study		
342-345		As with lines 301-302, please clarify that a formal change in the value of M1 or M2 is not intended. Rather, the assay sensitivity of the NI study may be questioned, if the active control performs substantially differently in the NI study than the chosen M1 would have predicted.	1
347-348	The material in parentheses may be interpreted as saying that the active control must have had an effect of at least M1 in the NI trial in order to confirm assay sensitivity. This is likely not what is intended here, and the material in parentheses could be deleted without loss of meaning.	Please revise this sentence to read, "As noted above, the choice of M1, and the decision on whether a trial will have AS, is based on three considerations..."	3
356-357	The material in parentheses can be deleted without loss of meaning.	Please revise this sentence to read, "...a specific active treatment regularly showed this treatment to be superior to placebo (or some other treatment)."	3
360-363		Please expand this portion of the Guidance to indicate whether there are specific standards that should be adhered to regarding the conduct of meta-analysis of historical studies. For example, later in the document and in the examples, random study effects are routinely referred to. Consider whether there are other analysis standards that should be mentioned.	2
399-411		This paragraph could be condensed, making the Guidance shorter.	3
400		Please reword to "will have been evaluated similarly to", as this refers to historical data.	
432-444	The message in this section is extremely important and should be considered for inclusion in a	Please consider for inclusion in a summary section that highlights key points from the guidance.	1

	summary section that highlights key points from the guidance.		
439		Please introduce "intent-to-treat" in a glossary or early in the document and then use "ITT" thereafter.	3
447	The term "perverse" has a negative connotation and can be deleted without loss of meaning.	Please revise this sentence to read, "...the incentives in an NI study are quite different from those in superiority trials."	3
448-449	Suggest moving the term "In general" to the beginning of the previous sentence beginning with "In a superiority trial", as this term applies to this entire section.	Please move the term "In general" to the beginning of the sentence.	3
457	Suggest inserting "At a minimum, " at the beginning of the sentence to be consistent with the messaging of the rest of the guidance.	Please insert "At a minimum" at the beginning of the sentence.	3
479	It is helpful to include alternative designs in the Guidance, so the audience first ensures that an NI design does in fact meet its development needs. However, inserting this material this late in the document causes confusion about whether these alternative designs are a type of NI design.	This material should be placed earlier in the document so that the remainder of the document deals directly with NI designs only.	2
487-495		We presume that additivity rather than synergy is implied here, but it would be helpful to make that distinction explicit.	2
547-549	There are situations where drugs are not pharmacologically similar but are still candidates for a NI design rather than an add-on design. This portion of the Guidance seems to discourage that approach.	Please expand this portion of the Guidance to explain why drugs that are not pharmacologically similar should generally not be considered for study in an NI design.	2
571-573	It is noted that a value of M2 that is 40% of M1, with a test at the 1-sided 0.025 level, roughly corresponds to use of 1-sided 0.001 in a superiority trial. As a consequence of this, would a 99.9%	Please specifically mention using a 99.9% CI with the full value of M1, if that is an acceptable approach.	2

	CI with M1 as the reference be another method for showing effectiveness?		
596		Please define "AMI" in a glossary or at the first time it is used.	3
597-598	Why is the multiplicity situation "not well defined" in this case? Testing NI first and then superiority on the other endpoint is a fixed sequence method. If both endpoints are primary, then other statistical approaches could be used. Is this the distinction that was the focus of this remark? If more complex situations were envisioned, such as gatekeeping procedures when there are two or more dimensions to the set of testable hypotheses, then it would be helpful to mention these as possibilities.	If methods other than fixed sequence are being referred to here, please mention those.	2
604-606	The dangers of deciding on a margin with data in hand are understood, but lines 301-302 seem to suggest doing this.	Please modify this portion of the Guidance to make it clearer that the margin is not being changed, but rather the assay sensitivity of the study is being questioned.	1
617		Please add "... unless risk-benefit issues warrant the choice of a drug with a smaller point estimate of effect." to the end of this sentence.	3
624	For this document, the fixed margin method is considered synonymous with the 95%-95% method. However, other fixed margin methods have been used in the past. Therefore it would be helpful if the synonymous meanings in this document were presented very early in a more visible fashion.	Please define these two approaches as exchangeable with each other early in the document, such as in a special introduction section or in a glossary.	2
625	The word "method" at the end of the sentence should be removed.	Please revise this sentence to read, "This method is generally referred to as a fixed margin method and the 95%-95% method (or 90%-95% method, depending on the CIs used to calculate the NI margin)."	2

642-644	It is unclear why a more objective endpoint, such as mortality, should be subject to more conservative estimation.	Please provide additional rationale for the need for conservativeness for the mortality endpoint.	2

GUIDELINE SECTION TITLE: IV. CHOOSING THE NON-INFERIORITY MARGIN AND ANALYZING THE RESULTS OF AN NI TRIAL			
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**	**Priority**
663	Rewording to either "selecting the margin" or "performing the margin selection" would be advisable, as "selecting the margin selection" is redundant.	Please reword to either "selecting the margin" or "performing the margin selection"	3
687		Please change to "how the effect of the active comparator related to that of placebo", in order to avoid the juxtaposition "comparator compares".	3
689-691	To maintain consistency with the rest of the document, should this line end with "compared with placebo"?	Please revise this line to read, "...past studies of the control, compared with placebo."	3
710		Please reword to "Both approaches are discussed later in Section IV -----", as "sections of Section IV" reads awkwardly.	3
723-724	It is noted that the 95% CI method using past studies' data is "potentially flexible". Can examples of when this may be the case be provided?	Please modify the Guidance to describe examples of when this flexibility might be appropriate. Alternatively, provide a set of factors that would be important is making this determination.	1
768	It should be clarified whether this particular CI is 1-sided or 2-sided.	Please clarify whether the CI mentioned here is 2-sided, as is generally the case, or 1-sided which has historically been applied in some settings.	3
779-780		It might be mentioned also that assessment of heterogeneity of	2

		treatment effects might motivate the exclusion or down-weighting of some studies, when determining the value for M1.	
930-936	If the total N from historical studies is so large that the CI from the meta analysis is quite narrow, then the point estimate from a study may fall below the CI. Because of this, we question the use of the term "inappropriate" for this outcome.	Please delete this section, or provide further rationale for why this outcome would be considered inappropriate.	3
997		A glossary at the beginning of the document to define RR, HR, etc., is advisable.	3
1030-1036	This passage is an example of some redundancy that, if eliminated, would make the document shorter. The two margins presented here have been discussed previously in the document. If the intent is to have each section "stand alone", however, then the need for redundancy is understood.	Please consider deleting this section.	2
1050		Please clarify whether it is the NI or the M1 margin being referenced in this sentence.	2
1060-1062		Please also provide an example where the risk ratios varied across studies but the absolute differences were relatively constant.	2
1098	The meaning of "revisited" should be clarified. If sufficient *a priori* documentation of how study population differences will be accounted for in the analysis of the NI study, then there should be no need to alter the pre-specified margin after the study is complete.	Please clarify the meaning of "revisited" in this context.	2
1258-1259	This sentence may cause confusion. Even though the exact value of the margin is not explicitly stated for the synthesis method, the point estimate	Please delete or reword the sentence that reads, "In the synthesis approach, the NI margin is not predetermined..."	2

	from the historical data, its standard error, and the fraction of it that must be retained by the test drug are all implicit in the synthesis method, so that a sample size can be calculated for the NI study to have a given power. This sentence suggests that the margin is determined after the NI study is complete.		
1271-1274		Please provide one or two examples of how a trial might have violation of assumptions for the synthesis test.	2
1291-1293	It is not clear why the lack of prespecification of M1 for the synthesis method is a disadvantage. For the synthesis method, the fraction of the effect of the active control to be retained is prespecified, and the observed effect of the active control is obtained from previous studies. Both of these quantities are used directly in the test statistic for the NI trial. Therefore, a "*de facto*" value of M2 is implicit in the test statistic.	Please explain why the lack of prespecification of M1 for the synthesis method is a disadvantage.	1
1295		A period is missing at the end of the sentence prior to "As also noted..."	3
1323-1324	The meaning of "when this is the case for M2" is not clear. Does this refer to the situation where the study is successful with respect to the M2 margin but not with respect to the M1 margin? If so, it should be pointed out that this will occur because of differences between the nature of the synthesis vs. fixed margins methods, as M2 is by definition smaller than M1.	The Guidance should state that this outcome will occur because of differences between the nature of the synthesis vs. fixed margins methods, as M2 is by definition smaller than M1.	2
1332-1352		Please consider modifying the Guidance to include a similar section for the synthesis method.	2
1348-1349	Given the subtleties of adaptive trials, it may be best not to try to cover sample size adjustment in this guidance, but to	Please consider deleting this sentence.	3

	reference the adaptive design guidance.		
1363		Please correct the typo regarding left vs. right parentheses.	3
1365-1366	The term "fatal" has connotations beyond its meaning.	Please reword to "many kinds of problems that can render a superiority trial unsuccessful, such as ..."	3
1370-1371		We suggest the Guidance indicate whether an "as-treated" analysis fully corrects for these concerns, or whether a "per-protocol" analysis is sometimes needed, to address target population issues,	1
1372-1374		The remark here regarding performing both ITT and as-treated analyses should also be considered for the section on "Good Study Quality" (starting on line 430).	2
1378-1381	It is understood that an open label design raises concerns in any study, but it is unclear why it is of more concern in the NI setting than in the superiority setting.	Please explain why an open label design is of more concern in the setting of an NI design, relative to a superiority design.	3
1383-1403	Given the subtleties involved in adaptive trials, it may be best not to try to cover sample size adjustment in this guidance, but to reference the adaptive design guidance. In particular, Lines 1399-1403 appear to suggest that the DMC be involved in the adaptations of such studies. The draft adaptive design guidance stresses that the DMC can be involved in operationalizing the adaptations, but should not be involved in making the adaptive decisions.	Please reference the adaptive design guidance but do not attempt to address the issue directly in the noninferiority guidance.	3
1403		We suggest referencing this Guidance by its exact title.	3
1421-1429		Please explicitly reference the closure principle as a method to deal with these multiplicity	

		issues.	
1433-1434	The term "fatal" may have connotations beyond its meaning.	Please reword to "...errors that would lead to the failure of a superiority study, can lead to..."	

GUIDELINE SECTION TITLE: V. COMMONLY ASKED QUESTIONS AND GENERAL GUIDANCE			
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**	**Priority**
1486-1490	This material provides an example of apparent confusion regarding what approaches are to be taken. Here, the synthesis method and the fixed margin method are to be applied to the M2 and M1 margins, respectively. However, earlier in the document, such as in Figure 3, other approaches are described.	Please establish as early as possible in the document, such as in Section 4, what the recommended approaches are. Then harmonize the rest of the document to align with those proposals.	1
1492-1515	This section does not comment on the appropriateness of Bayesian methods for analysis of the NI trial itself. It would be helpful to clarify FDA's position on this here.	Please discuss the Agency's position on the appropriateness of Bayesian methods for analysis of the NI trial itself.	3
1517-1520		Please indicate here whether an unapproved drug (or a drug approved at a different dose or for a different indication) can be used as an active control if the approved drug cannot be used as the control for some reason.	1
1597-1599		Please mention that in this case the label would likely restrict to failures on the established therapy.	3
1620		Please modify this portion of the Guidance to provide a specific definition or examples of "outcome endpoints." The definition should specify whether these are mortality or major	3

		cardiovascular events, rather than pharmacologic endpoints.	

GUIDELINE SECTION TITLE: V. APPENDIX--EXAMPLES			
Line Number	**Comment and Rationale**	**Proposed change (if applicable)**	**Priority**
1722	A random effects model was mentioned. It should be clarified what the random effect is (study, for example). Also, if there are a very small number of historical studies, the impact of the use of a random effects model on the confidence interval should be considered before uniformly recommending that such models be used in this setting.	Please clarify whether the random effect is the study effect. Also, clarify if there are cases where using random effects models may not be recommended.	2
1732	In this example, the log of the risk ratio was used to obtain the value of 1.378. In an earlier example, a linear version was used. Are there principles to guide which scale is preferred?	Please provide guidance on when linear vs. ratio scales are preferred.	3
1772-1775	The distinction made between the fixed margin and synthesis methods, regarding pre-specification of M1, may be blurred by the fact that the estimate of the effect of active control from historical studies enters explicitly into the statistical test performed in the NI study. Are there other factors that make this distinction important? If so, these should be mentioned.	Please provide additional rationale for making this distinction between the fixed margin and synthesis methods.	1
1798	1.02 is stated to be the log of 0.527. However, it is actually the log of 0.361. Is this simply a typo, or was the log of 0.527 intended to be used here?	Please correct the value if it is a typo. Otherwise, provide rationale for the use of the confidence bound of 0.527 rather than the point estimate of 0.361.	1
1779-1781		It would be more accurate to say "the upper confidence bound for the Warfarin effect M1 was estimated ----"	3
1986-	Lines 1986-1990: Given the acknowledged bias in the placebo estimate, it should be	Please consider using a different example to	3

1990	considered whether two "halvings" of the 29% are justified in this particular example.	illustrate the guidance's point.	

Conclusion

Thank you for this opportunity to comment on the draft guidance on *Non-Inferiority Clinical Trials*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Katie McCarthy
Director, Science & Regulatory Affairs
The Biotechnology Industry Organization (BIO)