

Document Title: Draft Guidance for Industry on Non-Inferiority Clinical Trials [Docket No. FDA-2010-D-0075]	ISCB Vaccine Subcommittee	Date: 20-Apr-2010
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Page/ Section/ Paragraph/ Line No	Comment type *	Reviewer name	Comment (with rationale)	Proposed change
General comments				
	N	GSKBio	The document covered different aspects of non- inferiority clinical trials in particular for pharmaceutical products. Some other areas are not represented.	Some examples using biologicals (especially in vaccine trials) and/or safety could be included to enrich the text and showing broader applications.
	M	GSKBio	When refer to p-values, there is not always mention if this is a one sided or a two sided.	Please clarify
	N	GSKBio	The guidance is specially focused to establish a non inferiority margin in case of efficacy studies.	Some guidance on safety would be useful. In that case, M2 only is usually defined and can be moving according to the rate. More frequent event could lead to a larger clinical margin (referring to Kem Phillips method) Please consider to expand in some extend) .
	N	GSKBio	To finalize the parallel between superiority & non inferiority, the concept of M2 could be introduced in the superiority as the minimum clinical efficacy required. This concept is a standard in prophylactic vaccines	To add this concept in section III.A.1.
	N	Scott Patterson	The discussion of III.A.1 is overly complicated and not at all transparent to an un-initiated reader. Superiority is simply a special case of non-inferiority where M1=M2=0 and the NI alternative/null hypotheses are reversed. Both are valid approaches, but there has been a whole lot more superiority testing than NI testing historically.	To clarify this concept in section III.A.1.

	N	Scott Patterson	Guidance should be provided in this document on acceptable approaches to the design NI studies with multiple primary endpoints. Use of the intersection-union procedure is ill-advised in many such settings.	Some guidance on this would be useful.
	M	Scott Patterson	Repeated references throughout the draft guidance are made to `assay' sensitivity when it is `trial' sensitivity that is meant (e.g. line 231). As assays are generally always used in such studies, the guidance should be clarified to ensure that trial sensitivity is what is of interest.	Please clarify.
	N	Rick Chappell	Little mention is given to the scale of the margin (e.g., multiplicative vs. additive) even though it also has large implications.	Some guidance on this would be useful.
	N	Julia Singer	Throughout the guideline it is assumed that the CIs of different parameters are always equally tailed. In the chapter "Logic of the NI Trial" the lower bound of the two-sided 95% CI is considered to be equivalent to the lower bound of the one-sided 97.5% CI. There are quite a lot of CI methods for which this is not true.	Please clarify.
Specific comments				
Page 1 Footnote 2	I	GSKBio	The footnote refers to "therapeutic" biologic but does not include prophylactics	Eliminate the word "therapeutic" and replace by "biological products"
Page 4 Line 123	I	GSKBio	The statement "study perhaps too small" is related with sample size and power and is not adding any value here	Delete "(study perhaps too small)"
Figure 2	N	GSKBio	The figure could be completed to covered the most frequent situations.	Add a case "7" in the figure where the point estimate lies between 0 and 1 the lower limit between -1 and 0 and the upper limit between 1 and 2
Figure 2	I	Scott Patterson	Figure 2 is not correct. There is always the possibility that C-T is indistinguishable or marginally above M1 but greater than 0 or that C-T statistically exceeds M1.	Please revise.
Page 5 Line 158	N	Scott Patterson	This outcome is not at all unusual, and the FDA guidance should provide guidance on how to interpret such results and how bio-creep to placebo will be avoided. Combination drug products would also be expected to show such characteristics if absorption were altered slightly by mixing of the separate drugs relative to separate administration, etc.	Consider to add this in the text

Lines 164-165	I	GSKBio	The sentence "It must be estimated (really assumed)" can be confusing	Replace by "it must be assumed based on ..."
Page 9 Line 326	I	GSKBio	It is not clear what the authors means by "but unacceptable loss of the control effect".	Please clarify
Page 5	N	GSKBio	It may be good to revisit fig 2 with M2 to ensure there is no misunderstanding. If M2 is specified there should be no interpretive problem for case number 6.	Consider to add this in the text
Page 4 Figure 1	I	Scott Patterson	Figure 1 is not correct. There is always the possibility that T-P is either marginally inferior or statistically inferior to 0.	Please revise.
Page 4 Figure 1	I	GSKBio	Cases 2 and 3 are not really distinct as presented	Please clarify that in one case the estimated value is zero versus non zero, even if the lower limit of the CI is below zero in both situations.
Page 12 Line 447	I	GSKBio	The concept of compliance be lead to misunderstandings	Please be more explicit; the poor compliance has a biased impact on non-inferiority. Does that mean that the margins should be reconsidered when the quality of the study is poor?
Page 16	N	GSKBio	The choice of the active control could be expanded	The one with the corresponding highest point estimate of effect should ordinary be used. Therefore, shouldn't we take into account the CI? Please clarify.
Page 22	N	GSKBio	Ref : "determining HESDE from single study vs. multiple trials". Multiples trials evaluation allows the opportunity to evaluate an overall estimate of the treatment effect of the active control as well as a measure of the study-to-study variability of that treatment effect.	This is also feasible in a single study by defining subgroup. This can be explained.

Page 11 Line 285	I	Scott Patterson	The statement, `Note that the clinically acceptable.....' appears to conflict with previous statements – e.g. O'Neill, R. T. (1997) Secondary endpoints cannot be validly analysed if the primary endpoint does not demonstrate clear statistical significance. Controlled Clinical Trials, 18, 550-556.	Please provide additional guidance on what criteria would need to be met.
Page 22 Line 894	T	Scott Patterson	`can' should be replaced with `should'	Please correct.
Page 22 Line 905	N	Scott Patterson	References should be added for appropriate meta-analytic strategies.	Please add references.
Page 23 Point 3 Line 930	N	GSKBio	Pooling of large outcome studies; when saying it would be inappropriate to have the point estimate for one of these fall below the 95%CI lower bound of the pooled study data. CI for the considered point estimate of a single study could be much larger than CI for the pooled estimate and so this would be not justifiable to consider that point estimate as inappropriate	A clarification is needed.
Page 23 Point 4 Line 944	N	GSKBio	The authors suggest to use the largest effect (point estimate) regardless of the CI around that estimate. This is not in line with the 95%-95% or 90%-95% methods described on page 28	A clarification is needed.
Page 24 Section c	N	GSKBio	The authors suggest different metric for treatment effect. More sophisticated metric, for instance accounting for an effect that would depend linearly on the event rate in the control group, could be used.	Add a less traditional metric which led to the NI approach developed by Kem F. Phillips (Statist. Med. 2003; 22:201–212) could be mentioned
Page 28 Line 1163	I	GSKBio	"the study quality would not affect M2 when it is very small compared to M1". Some precision should be given	What does "quality" means here? Compliance? What does "very small" indicates? Any idea of relative magnitude? Please clarify.
Page 32 Line 1324	T	GSKBio	Ref: "There is also a difference in implication when the study NI conclusion is "not quite" significant (M1 is not included) for M1 and when this is the case for M2. "	It seems that M1 and M2 are reverted in the sentence

Page 34 Line 1414	T	GSKBio	level of no more than 5% should be 2.5% (?) in addition to that line 1411 specify a two-sided CI ?	Please verify the levels across the document.
Page 36 Lines 1513 to 1515	N	GSKBio	In which situation heterogeneity of covariate may increase the variance? Is this related with the use of random effects model?	This could be re-wording: situation where there is heterogeneity of group difference (or treatment effect) among covariate, the variance may be increased
Section G	N	GSKBio	Role of Adaptive Design in NI studies	To consider to move to the guidance for adaptive design.

* Please use **M** for Major, **N** for Nice to Have, **I** for Information or requiring clarification, or **T** for Format or typing error