27 June 2017

Submission of comments on 'Guideline on multiplicity issues in clinical trials' (EMA/CHMP/44762/2017)

Comments from:

Name of organisation or individual
German Region of the International Biometric Society (IBS-DR) and German Society for Medical Informatics, Biometry and Epidemiology (GMDS)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Multiplicity issues arising from interim analyses are not discussed in the guideline. Instead, reference to the "Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design" is given. Although we recognize that recommendations already given do not have to be repeated in detail, we feel that a short summary of the relevant aspects of multiplicity adjustment for interim analyses should be included in this guideline.	
	Reference to ICH E17 "General principles for planning and design of multi-regional clinical trials" should be given, and multiplicity in multiregional trials occurring from e.g. multiple endpoints or analyses due to different regional requirements should be discussed in this guideline.	
	The recommendations concerning multiple primary endpoints, key secondary endpoints for which additional claims are desired, and composite endpoints could be structured in a better way. They are spread over three different sections (5.1, 6., and 9.) which results partly in redundant and partly in ambiguous statements (see specific comments below). The guideline could be substantially improved by a joint discussion of these three aspects in only one newly structured section. In this context, the distinction between multiple primary	

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	and key secondary endpoints is questionable. When multiple endpoints exist for which an efficacy claim is strived for, they are sometimes called multiple primary endpoints and sometimes called secondary endpoints which may become the basis for additional claims. What is the difference? It could be easier to just discriminate endpoints for which a confirmatory conclusion is needed and which are therefore to be included in a multiple testing procedure from endpoints for which no claim is intended and confidence intervals and analyses are of descriptive nature only.	
	In the context of multiple endpoints which are analysed separately and composite endpoints which reduce the dimension of multiple endpoints to one statistical test, the role of multivariate analysis procedures incorporating the correlation between multiple endpoints should also be discussed and recommendations on its appropriateness for confirmatory conclusions should be provided.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Line 122-124		Comment: “The CHMP Points to Consider on Application with 1. Meta-analyses and 2. One Pivotal Study (CPMP/2330/99) covers the situation when the type I error needs to be controlled at the submission level where more than one confirmatory trial is included in a submission.” We do not see how this is covered by the mentioned PtC and we wonder whether control of the type I error is necessary in this situation as usually all trials have to be positive. Proposed change (if any): Please explain in more detail.	
Line 196-198 Line 474-475		Comment: Line 196 to 198 in section 5.1 on multiple primary endpoints, suggest two possibilities of "study success" both requiring to statistically establish "positive outcome" in at least one endpoint. In contrast, section 9 discusses composite endpoints, whose "successful" analysis does not clearly require a statistically significant outcome with respect to any single component of the composite (presumably the phrases "beneficially affect" (line 474) and "affect negatively" (line 475) refer to trends rather than definite inferential conclusions). Proposed change (if any):	

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		The guideline would be improved by a joint discussion of multiple endpoints and composite endpoints within one section as proposed in our general comments. More explicit statements should be given to what extent statistical conclusions on single components of endpoints are expected.	
Line 273		Comment: “It is also important in this case that there is no inflation in the type I error.” The implication of this statement is not quite clear. Does this want to say that blind review ensures type I error control per se or does this mean that following blind review appropriate methods are required for control the type I error? Proposed change (if any): Please change wording to improve clarity.	
Line 379-389		Comment: These two paragraphs in 6.1 in fact do not relate to the topic of section 6.1 “Secondary endpoints expressing supportive endpoints” but they relate to the situation discussed in section 6.2 “Secondary endpoints which may become the basis for additional claims”. In chapter 6.1 they can lead to confusion and should therefore better be integrated in section 6.2. Proposed change (if any): Integrate the statements in line 379-389 into section 6.2.	
Line 426-428		Comment: The paragraphs written in italic letters in the beginning of	

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		each section are usually a summary of the section. The sentence in line 426-428 “A licence may be restricted if unexplained strong heterogeneity is found in important sub-populations, or if heterogeneity of the treatment effect can reasonably be assumed but cannot be sufficiently evaluated for important sub-populations.” does no longer constitute a summary of this section on subgroup analyses, since in the current version of the guideline the respective statements on evaluation of homogeneity of treatment effects across subgroups were removed and only a reference to the new subgroup guideline is given. Proposed change (if any): Re-formulate the summary of this section. Also in the title “… restriction of the licence to a subgroup” could be dropped since this is not covered by the section.	
Line 482		Comment: “The other type of a composite variable arises in the context of survival analysis.” Other types of composite endpoints are not exclusively survival endpoints (e.g. composite binary endpoints etc.). Proposed change (if any): Re-formulate appropriately.	
Line 515-519		Comment: “Whilst it may often be reasonable, a priori, to assume that no component of a composite relating to efficacy will be adversely	

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		affected, 'net clinical benefit' endpoints are employed to investigate whether beneficial effects are offset by increased detrimental effects. Because of the assumptions made in 'weighting' the components and in the overall interpretation, such composites will not usually be appropriate primary endpoints." The message of these sentences is unclear. Is it recommended to employ 'net clinical benefit' endpoints to explore the assumptions of no adverse effects? Or does this mean that 'net clinical benefit' endpoints are discouraged? Proposed change (if any): Please be more specific in this recommendation.	
Line 594-599		Comment: Line 594-596 state "If the confidence regions do not correspond to the hypothesis testing procedure, different conclusions are possible, e.g. a confidence interval excluding the null hypothesis combined with a non-significant testing result or vice versa." We think that this situation should be avoided, and understand line 594-596 in this sense. Does the following advice in line 596-599 "The decision should, however, be based on the hypothesis test. In that case it is advised to use simple but conservative confidence interval methods, such as Bonferroni-corrected intervals, ensuring that the uncertainty about the beneficial effects is properly understood." mean that also the test procedure should be based on Bonferroni correction in order to avoid the	

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		situation of inconsistent conclusions? Proposed change (if any): The guideline should be more explicit in this recommendation.	

Please add more rows if needed.