<28th of march 2011>

Submission of comments on 'Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available' (EMA/759784/2010)

Comments from:

Name of organisation or individual
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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)*
	The German Medical Association supported by its Commission on Drugs is grateful to have been given the opportunity to comment on the 'Reflection paper on the need for active control in therapeutic areas where use of placebo is deemed ethical and one or more established medicines are available'. The reflection paper deals with a very important issue. In view of recent discussions on the most appropriate type of clinical studies, it is also timely to ask for comments and exchange arguments with the aim of reaching mutual understanding and agreement within Europe.	
	Generally, placebo-controlled trials are seen as acceptable in cases (i) without specific treatment options (ii) short term treatment of mild diseases (e.g. mild essential hypertension without end organ damage) (iii) diseases with high responder rates to placebo. From a scientific point of view, the three-arm trial has major advantages, particularly in defining the place of the new drug as compared to available treatment. A key issue is the identification of the 'accepted' standard therapy and the choice of dose, which may vary from country to country and even within a country among	

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	specialist physician societies depending on the type of patient concerned. It should be considered that the three-arm trial has the same ethical implications as placebo-controlled trials because it contains a placebo control arm. The use of placebo may expose the study participants to increased risk from not receiving active treatment (see above). Placebo-controlled trials may require a smaller overall sample size than trials comparing a new drug with an active therapeutic agent. However, in a three-arm trial a higher number of patients is required to demonstrate superiority of the new experimental medicine over standard treatment. The German Medical Association sees specific ethical problems in including patients unable to give consent (e.g. minors, disabled persons) in placebo-controlled trials which have not been addressed in the reflection paper so far. Thus, we expect this issue to be included and specifically discussed. The validity of indirect comparisons is controversially debated. However, in the context of a broader assessment of several treatment options where a direct comparison is practically unfeasible, indirect comparison is a valuable and necessary tool. Hence, we see a need	

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	to address this specific question. Indirect comparison may also be the option of evaluating treatments for rare diseases where the number of patients is so low that a three armed trial would be not feasible. On the other hand, in therapeutic areas with a high success rate (> 95 %), it could be discussed whether controlled trials are necessary at all. This option has not been discussed at all.	
	We would like to suggest an introductory chapter to the reflection paper in which the points made above are discussed.	

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)*
23		Proposed changes: Drop the word "three-arm" in the phrase "Where feasible, three-arm trials …". Trials with several doses of the new medicine and/or the active control are also covered by this reflection paper.	
27		Comment: It is unclear in which cases a placebo-controlled study that is deemed ethical is not feasible. Proposed change: The word 'feasible' should be deleted.	
28-29		Comment: The term 'case-by-case' should be replaced because of the ambiguity of criteria. Proposed change: The need for an active control should be judged by means of a catalogue of pre-specified criteria.	
36		Comment: The comparison to active control should not only "usually" be direct. Proposed change: Delete "usually" and add "if possible" as the last two words in the sentence.	
52		Comment: (Outside the scope of this paper): Usually active control therapies are determined after consultation with the competent authorities. However, an active control therapy that might be an established therapy in one region may not play the same role in another region. A decade after the ICH process more and more divergent opinions emerge. Even	

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		within Europe there might be ambiguity about what an established therapy is and it is not desirable that sponsors be led into "regulatory" traps.	
53		Comment: Please clarify why the role of comparisons to active control in the benefit-risk decision is not within the scope of this guideline. In the EMEA Position Statement 17424/01 it is stated that "granting marketing authorisations to new medicinal products when their benefit to risk balance is at least the same as that of established therapies, if any, is a basic public health principle. These criteria form the basis of the CPMP's scientific opinion." This means that a scientific decision by the CPMP must be made about the new medicinal products benefit to risk balance in comparison with established therapies. It is the view of the German Medical Association that trials comparing a new medicine with concurrent active control play a central role in the decision making process. Otherwise studies may be performed with active control but without proper sample size planning based on the reasoning that comparisons with active control are only "explorative". Sponsors should be urged to fully exploit inferential analysis strategies when this is possible without type I error adjustments (alpha splitting).	
81		Comment: This sentence should be rephrased. In our opinion assessing benefit-to-risk relations depends at the very least on a comparison with placebo or active control. If this data is not available, accurate assessment is most probably impossible.	

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86		Proposed change: replace 'difficult' with 'impossible'	
104		Comment: see comment for line 27	
121-125		Comment: The German Medical Association sees a place for historical data sets as comparators. However, the given example sounds speculative and is not supported by evidence.	
142		Comment: The need for an active control should be emphasized. In cases where established therapies exist, it is the absence of an active control which needs to be justified on a case by case basis, whereas the presence of an active control should be the rule. Proposed change: A placebo-controlled and active controlled trial is the rule. The absence of an active control needs to be justified based on the catalogue of criteria exemplified in lines 28-29.	
146 ff.		Comment: We do not question that the two situations described are particularly important for the inclusion of a concurrent active control. Due to the limited knowledge of the properties of the new medicine, the concerns mentioned support the routine inclusion of established therapies within clinical trials with new treatments.	
154 ff.		Comment: It is widely known that sponsors run an additional risk when not including an active control. The recommendation for the inclusion should, however, be	

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		stronger. Sponsors who do not include an active control arm although established therapies exist should substantiate in the study protocol why the inclusion of an active control is deemed unnecessary.	
205		Comment: A literature review has a high potential for publication bias and selective reporting. Therefore, a systematic review is needed to reduce these biases. Proposed change: 'based on a systematic review' and further define what is meant by "systematic".	
207-209		Comment: It should be further explained what standards must be applied to allow historical studies (e.g. RCTs whenever possible) to be considered as an adequate alternative.	
225 ff.		Comment: The section addressing various objectives that can be pursued in clinical trials including an active control and placebo would benefit from more input from a biostatistical point of view. The presence of at least three treatment groups in confirmatory trials implies that multiple statistical tests and the construction of multiple confidence intervals need attention and possibly appropriate adjustment. Several multiple testing procedures have been described in the literature for this situation. Lines 238-239 of the draft reflection paper mention hierarchical procedures briefly, however this is just one procedure in the biostatistics toolbox. In line 226, two of the most common primary objectives for ERP trials with an experimental treatment (E), reference active treatment (R), and placebo (P) are used (i) to	

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		demonstrate superiority of E over P and (ii) to demonstrate non-inferiority (or equivalence) of E in comparison to R. Without the demonstration of superiority of E over P, a market authorisation is not possible, and the demonstration that E does or does not compare unfavourably with R is usually important information for the judgement of the benefit-risk balance. Regarding the demonstration of assay sensitivity, the draft of the reflection paper takes the view that "*requirements to establish assay sensitivity are usually equivalent to the requirements to show superiority to placebo for the active treatments*". This is understood to mean that both the active control and the new medicine must show superiority over the placebo. In section 1.5 of ICH E10 it is stated differently: "*When two treatments within a trial are shown to have different efficacy (i.e., when one treatment is superior), that finding itself demonstrates that the trial had assay sensitivity.*" This supports the assumption that assay sensitivity is already present when objective (i) is satisfied, i.e. when the experimental treatment demonstrates superiority over the placebo. This view is of particular interest in therapeutic areas where there is a high failure rate (e.g. studies in depression). In lines 88 – 96, the draft reflection paper discusses this and mentions some scenarios: If both, E and R are superior to P, this certainly is the most satisfactory scenario for the demonstration of assay sensitivity. However, during planning there is considerable uncertainty about whether or not such an objective can be achieved and a sequential approach	

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		starting with either the comparison E versus P or R versus P could provide more confirmatory statistical evidence. If both, E and R fail to demonstrate superiority over P, this leads to the conclusion that the trial lacks assay sensitivity, and it leaves the question open as to whether assay sensitivity could be demonstrated in a new trial with a more appropriate design. If E fails and R does not, this usually leads to the assumption that E is not effective. Regarding the scenario: R fails and E does not, the draft of the reflection paper is silent on this point. E could, for example, be superior to both R and P. Note that in a hierarchical test procedure that starts with the comparison R versus P and fails to demonstrate superiority, the sponsor cannot gain any advantage from an apparent positive result in the comparison E versus P or E versus R. The last two scenarios (i.e. either E or R fail) have a considerable probability of occurring merely as a result of chance, even if the assumptions underlying the sample size estimation are true and power for each single comparison is high. A requirement for demonstrating superiority of E and R over placebo simultaneously would also affect confirmatory results on the otherwise successful comparison. A similar statement can of course also be made if the variable of interest is a safety variable.	
271		Comment: Link doesn't work and has to be updated Proposed change: Update the link.	
Flow chart		Comment: The flow chart raises the questions mentioned	

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		previously.	

Please add more rows if needed.