EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9th 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
EFSPI [European Federation of Statisticians in the Pharmaceutical Industry www.efspi.org]

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).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Comment: The draft guideline does not point to already existing European disease specific guidelines (PtCs, etc) where 3-arm studies are required or strongly recommended. Further to this argument one would very much welcome more directives about when three (or multi)-arm studies are more or less necessary and when this is less important. Proposed change: Make clear which arguments in this guideline are still valid and can be transferred when the primary variable is not efficacy but safety	
	Comment: The primary objective(s) is a driver of the study design. A study needs to be properly powered in order to address the study objective(s). Though a 3 arm study will aid inference (line 89), one may not be able to reach definitive conclusion through an underpowered study. The reflection paper does not comment on the sequence of comparisons among the 3 arms, and how to best address multiplicity issue. It is in fact silent on the analysis perspective in a 3 arm trial. The multiplicity issue could be very complicated due to the issues related to the primary endpoint vs the secondary endpoints and non-inferiority vs superiority. This topic is critical and needs to be addressed. Proposed change: Provide further clarification of the study objectives driving the study design, and address	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	aspects of multiplicity issues in 3-arm trials.	
	Comment: Interpretation of the result may not be straightforward in a 3 arm trial. For example, when the active control arm failed to demonstrate assay sensitivity through the comparison to the placebo arm in a 3 arm trial, it is unclear how to interpret the result that the experimental medicine is shown to be superior to placebo. Proposed change: Provide further clarification on interpretation issues with 3-arm studies, in particular in the absence of demonstrating assay sensitivity of the active control to the placebo arm.	
	Comment: It is unclear, in this document, how the direct comparison to active control are used to evaluate the benefit/risk ratio of a new product, i.e. to "gauge and understand the magnitude of benefit or risk". It is probably the subject of other regulatory documents or ongoing working groups. If so, references should be added if it is not possible to clarify this point in this reflection paper Proposed change: Add references to other documents or ongoing working groups relating to benefit/risk	
	Comment: For three-arm trials where the primary objective is demonstration of superiority to placebo, it is not specified (either page 7/9 or in the example dealing with studies in depression) how would be considered a study where the experimental treatment is superior	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	compared to placebo but the active control fails to distinguish from placebo. Could the positive character of the study be challenged by regulators? Proposed change: Clarify regulators viewpoint when this happens	

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 23		Comment and proposed change: 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.	
Lines 31-33		Comment: The phrase "active treatment to be discontinued" is not clear as it may refer to "active control". Proposed change: Rephrase to "experimental drug to be discontinued"	
Line 52		Comment: Define more precisely what is meant by the role of comparison to active control. 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 within Europe the might be ambiguity about what is an established therapy and it is not desirable that led sponsors into "regulatory" traps. Proposed change: clarify when a therapy is established and when this is not so clear.	
Line 53		Comment: same topic 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	

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)*
		of established therapies, if any, is a basic public health principle. These criteria form the basis of the CPMP's scientific opinion." This is understood as meaning that a scientific opinion by the CPMP must be made about the new medicinal products benefit to risk balance in comparison to established therapies. It is our view that the comparisons from trials of the new medicine with concurrent active control play a central role in the decision making process. Otherwise we foresee studies with active control but without proper sample size planning based on the excuse that comparisons with active control are only "explorative". A related further poor habit is when sponsors do not fully exploit inferential analysis strategies when this is possible without type I error adjustments (alpha splitting). Proposed change: Please clarify why the role of comparisons to active control in the benefit risk decision is not within the scope of this guideline.	
Lines 88-93		Comment: Assay sensitivity was mentioned here. It mentioned that an active-control arm is needed to facilitate assay sensitivity in a placebo-controlled study. At Line 236, it mentioned the placebo is required to ensure the evaluation of assay sensitivity in an active-control study. It would be helpful at least to mention the constancy assumption when referring to active-controlled study designs since it is an important concept. Proposed change: Please add further details on the constancy assumption	

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 146 and following		Comment: It is not disputed that the two situations described are particularly important for the inclusion of a concurrent active control. They are, however, difficult to foresee in the planning phase. Due to the limited knowledge of the properties of the new medicine the mentioned concerns are more a supporting argument for the routine inclusion of established therapies into trials with new treatments. Proposed change: an example would be helpful where in the past a new medicine with suspected handicaps has never the less been studied in phase III	
Line 149		Comment: The meaning of "treatment with inferior efficacy" is unclear while this point seems crucial to understand the regulatory considerations quoted. Proposed change: Clarify what is meant by this phrase	
Line 191		Comment: The "downgrading" of some rating scales and patient reported outcomes as just a means only useful for clinical trials and with little relevance in clinical practice for the patients is not fully understood. Actually this means that the benefit- risk balance for these products has a weak basis because the benefit for the patients' clinical practice cannot reliably be assessed. At a time where national health Technology Assessment agencies are making separate evaluations regarding the re-imbursement status it seems to be counter intuitive to allow for endpoints in clinical trials with limited relevance for the patients' clinical practice. Given that there were other endpoints with greater relevance to patients in clinical practice, these endpoints should replace the rating	

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)*
		scales in clinical trials. Proposed change: make clear that the measurements that are used in clinical studies based on recommendations from regulatory authorities bear clinical relevance and are not only of use in clinical studies.	
Line 225		Comment: Line 225 pp: the section on 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 implies for confirmatory trials that multiple statistical tests and the construction of multiple confidence intervals need attention and possibly an appropriate adjustment. Several multiple testing procedures have been described in the literature for this situation. In line 238/239 the draft reflection paper mentions briefly hierarchical procedures, but this is just one piece 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 (i) to 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 normally important information for the judgement in the benefit risk balance. Regarding the demonstration of assay sensitivity the draft reflection paper takes the view that "*requirements to establish assay sensitivity are usually*	

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)*
		equivalent to the requirements to show superiority to placebo for the active treatments". This is understood meaning that both, the active control and the new medicine must show superiority over 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 to assume that assay sensitivity is already present when objective (i) is satisfied, i.e. when the experimental treatment demonstrates superiority over placebo. This view is of particular interest in therapeutic areas where there is a high failure rate (e.g. studies in depression). In line 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 starting with either the comparison E versus P or R versus P can 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 open whether in a new trial and with a more appropriate design assay sensitivity can be demonstrated. If E fails and R not, this usually leads to assuming that E is not effective. Regarding the scenario: R fails and E not, the draft reflection paper remains silent. E could, for example, be superior to	

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)*
		both, R and P, and this would certainly be remarkable. Note, that in a hierarchical test procedure that starts with the comparison R versus P and fails to demonstrate superiority, the sponsor (who was possibly urged or advised in a regulatory context to accept R as an active control) cannot take 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 to occur just 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 affect also confirmatory results on the otherwise successful comparison. Proposed change: Provide further clarification on interpretation issues with 3-arm studies, in particular in the absence of demonstrating assay sensitivity of the active control to the placebo arm.	
Line 245		Comment: It mentioned that a formal comparison based on active control may not be necessary. If so, the results could be misleading due to lacking of power. Proposed change: Note how to address power issues in such situations	
		Comment: Is the flowchart (page 9) dedicated to trials where the primary objective is demonstration of superiority to placebo, or is it also applicable to studies aiming at evaluating a new compound versus a reference treatment? In the later	

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)*
		case, it is surprising to mention "Always include placebo control" whereas page 4 it is stated that a placebo is not requested if the aim is to establish the superiority to an established medicine. Proposed change: Clarify flowchart and reference to placebo	

Please add more rows if needed.