DETAILED GUIDANCE FOR THE REQUEST FOR AUTHORISATION OF A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES, NOTIFICATION OF SUBSTANTIAL AMENDMENTS AND DECLARATION OF THE END OF THE TRIAL , Draft Revision 3 (ENTR/F/2/SF D(2009)

COMMENTS FROM Les Laboratoires Servier

GENERAL COMMENTS

This Revision 3 of the Guidance provides useful additional recommendations aiming at harmonising processes among member-states however it should be clearly stated that 1/ the use of national language should be limited to documents given to the patients and national authorisation, 2/ substantial amendments are to be either submitted or notified to the Competent Authorities based on the current practices in several member states, 3/ the notification of the first visit of the first patient as required in the current EudraCT form.

SPECIFIC COMMENTS ON TEXT

Section	Comment and Rationale	Proposed change (if applicable)
2.1.4.2. Title	The title of the section "Amendments during the authorisation phase" should be replaced to avoid misunderstanding.	Replace "Amendments during the authorisation phase" by "Amendments during the evaluation phase"
2.1.4.2. 2nd bullet	Do not limit changes initiated by the sponsor to safety information. Eg adding new investigators?	Add a reference to the section on substantial amendment.
2.1.6.	To aim at a better harmonisation, the use of national language should be limited to documents given to the patients and national authorisation. Tables at the end of the current guidance are not attached in the draft and should be included since all member states have not disclosed such.	To be reworded
2.7. 5th §	The guidance referred to for CTD headings is not the good one.	
2.7.3. 2nd bullet	The draft requires the entry of the clinical trial performed in the third country unless justified. Delete the bullet since the justification may be assessed differently among member states.	Delete the bullet
2.10.	A copy of the opinion of the Ethics Committee of the Member state concerned has to be provided to the competent authority unless the Ethics Committee informs the sponsor that it has copied the competent authority. One objective of the revision is also to facilitate processes : there is a 'rational' for such request in case of late sequential application.	Delete the bullet

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3.3.	The directive and related guidances aim at harmonising procedures between member states. Among "substantial" amendments, some need a formal authorisation from the competent authority whereas others only require an information of the competent authority. To avoid additional workload from both competent authorities and sponsors, it is essential to introduce the two options that already exist in some member states.	Proposal : "A substantial amendment may be submitted to the competent authorities for authorization or information. This later case relates to amendment which do not require an assessment from the competent authority." eg change in insurance company, change in duration of study duration without change of the duration of exposure to the IMP … (see comment on section 3.3.1).
3.3.1.	State that adding/deletion a country should not be considered as a substantial amendment in the other member states concerned by the study. Same as for addition/deletion of investigators in the other member states concerned by the study.	Add a comment in the paragraph on "non-substantial amendment".
3.3.1. 4th bullet	The change in the definition of the end of trial has not always an impact on the scientific value of the clinical trial.	Replace "Change in the definition of the end of trial (this could significantly impact on the scientific value of the clinical trial)" by . "Change in the definition of the end of trial if it significantly impacts on the scientific value of the clinical trial"
3.3.1. 12th bullet	Replace the bullet stating that a limited lengthening of the trial time is a non-substantial amendment to the two following situations:	- "Change of the study duration without change of the duration of exposure to the IMP nor to the duration of treatment with the IMP, without change in the monitoring of the participants is a non-substantial amendment. In case of change in the monitoring of the participants, it is a substantial amendment".
3.5 (c) 1st bullet	Avoid duplication of work and require only "an extract of the modified documents showing previous and new wording in track-change version" when an amended document is provided.	Replace "An extract of the modified documents showing previous and new wording in track-change version, as well as the extract only showing the new wording." by "An extract of the modified documents showing previous and new wording in track-change version, as well as the extract only showing the new wording unless a stand-alone amended document is provided. "
3.5 (c) 2nd bullet	Once more duplication of work should be avoided. Based on the description of the change presented in the 1st bullet, the amended document should only states the date of the amendment.	Delete the last sentence.
3.10.	As stated in the current version of the guidance, before the Competent authority reach the decision to suspend or stop a trial, they must inform the sponsor except where there is imminent risk	Introduce this step at the beginning of the section.

SPECIFIC COMMENTS ON TEXT		
Section	**Comment and Rationale**	**Proposed change (if applicable)**
	and ask the sponsor and/or investigator for their opinion.	
4	The current EudraCT form requires the notification of the first visit of the first patient.	Create a section for the declaration of the first visit of the first patient.
4.2.2.	At the end of the section, clarify that a trial that is completed earlier due to a fast recruitment has not to be considered as an “early termination”.	Add clarification.