European Medicines Agency
<Unit>

31 August 2009

SUBMISSION OF COMMENTS ON

Commission Guideline on 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

COMMENTS FROM:

Name of Organisation or individual
AESGP – Association of the European Self-Medication Industry

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

Comments should be sent to the EMEA electronically and in word-format (not pdf).

1. GENERAL COMMENTS

Stakeholder No. *<to be completed by EMEA>*	**General Comment (if any)**	**Outcome (if applicable)** *<to be completed by EMEA>*

2. SPECIFIC COMMENTS ON TEXT

Line No of the first line(s) affected. *<e.g. Line 20-23>*	**Stakeholder No.** *<to be completed by EMEA>*	**Comment and Rationale; proposed changes** *<if changes to the wording are suggested, they should be highlighted using "track changes">*	**Outcome** *<to be completed by EMEA>*
1.1		**Comments:** We appreciate the clear statement reminding that national requirements might not exceed requirements from Directive 2001/20/EC and the deletion of the table with national requirements from the guideline. We hope this might in the long run reduce the requirement for national administrative documentation. **Proposed change (if any):**	
2.1.4.2		**Comments:** This section outlines that updating the application during the review (based on EC decision or new safety information that has become available) will restart the clock. Depending on national practice this could lead to an extension of review timeline.	

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		Proposed change (if any):	
2.5		**Comments:** Original text: *"The Version submitted should include all currently authorised amendments …"* – We understand that all amendments to the protocol after first authorisation of the trial shall be submitted, i.e. the latest version of the protocol. The situation can be that non-substantial amendments were made (thus no authorisation needed) or substantial amendments are under review by other authorities at the time of submission of a CTA. **Proposed change (if any):** *"The latest version of the protocol should be submitted ~~should~~ including all ~~currently~~ ~~authorised~~ amendments …"*	
2.8.3		**Comments:** Original text: *"If the applicant is the marketing authorisation holder and he has submitted an application to vary the SmPC, which has not yet been authorised, the nature of the variation and the reason for it should be explained in the covering letter."* It is unclear how to deal with the SmPC once a variation has been approved during the course of the study. **Proposed change (if any):** It is proposed to add an explanation to Section 3.3.2 and/or 3.3.3, 3rd bullet: *In cases, where a SmPC replaces partly or fully an IMPD or IB, substantial changes of the SmPC which might alter the initial risk to benefit evaluation may qualify as a substantial amendment.*	
2.8.5, Table 1		**Comments:** Original text: *The IMP is a placebo and the placebo has the same*	

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		composition, is manufactured by the same manufacturer and is not sterile. It is unclear what that means: "same" compared to what? **Proposed change (if any):** None, as clarification is needed.	
2.9		**Comments:** NIMPs: There has been a long discussion about NIMPs since the last guideline and the wording has been slightly changed. It still allows individual Member States to request documentation for NIMPs so there will probably be no major change in practice in the future. The "case-by-case" basis is problematic as it basically allows the HA to request additional documentation whenever they see fit. **Proposed change (if any):**	
2.9		**Comments:** Original text: *"When this is not possible, the next choice should be NIMPs with marketing authorisation in another Member State."* Like for an IMP with a MA in any a Member State or ICH country, the use of a NIMP with MA in an ICH country should also be recommended. **Proposed change (if any):** *When this is not possible, the next choice should be NIMPs with marketing authorisation in another Member State or ICH country.* *Where NIMPs without a marketing authorisation in the EU or in an ICH country are used …*	
2.10		**Comments:** The PDCO opinion and the EMEA decision documents contain sufficient information and details on all final agreements in terms of a paediatric development program. The summary report is a lengthy document with up to 100 pages or more, which is outdated as soon as PIP modifications have been applied	

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		for and approved. Even for MAA dossiers, inclusion of only the latest version of the PIP decision is required. Thus, we do not concur with the requirement to submit the PDCO summary report for the purpose of evaluating a CTA. **Proposed change (if any):** ~~*The*~~ *Paediatric Investigation Plan ("PIP"):* ~~*summary report*~~*, the opinion of the Paediatric Committee and the latest decision of the EMEA.*	
3.3		**Comments:** The list of amendments that may potentially be considered as substantial previously was an attachment. The list has now tremendously changed. It is unclear whether elements which were removed are now seen as non-substantial. Examples: In-/exclusion criteria, duration of exposure, change in posology, change of comparator. **Proposed change (if any):** None, as clarification is needed.	
3.3.2 /3.3.3		**Comments:** The list with examples of substantial and non-substantial amendments: the reference to CHMP/QWP/185401/2004 may not be immediately noticed. **Proposed change (if any):** As the reference to CHMP/QWP/185401/2004 is linked to the IMPD, the last paragraph of Section 3.3.3 is proposed to be shifted up to become the last paragraph of Section 3.3.2.	
3.6, 4th paragraph		**Comments:** Original text: *The response time may be extended…*the wording is weaker than in the previous guideline. This might open the door for HA to extend timelines in general. **Proposed change (if any):**	

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4.3		**Comments:** Original text: *The clinical trial summary report is part of the end of trials notification. However, the clinical trial summary report can be submitted subsequently to the end of trials notification.* Directive 2001/20/EC requires notifying the end of a trial within 90 days, but does not require a summary report to be submitted at the same time as the end of trial notification. With the above wording, it is our concern that authorities may insist on receiving the summary report within 90 days. The current version of the CTA detailed guidance requires a submission of a summary report within one year (expedited to 6 months for according to paediatric regulation), which is a reasonable and workable time frame. "End of trial" is usually defined as last patient last visit. Data Management, queries and data cleaning until data base lock as well as the subsequent statistical analysis of data would not allow drafting a full summary in an ICH E3 format in a 90 days time frame. Thus, the summary report will always be submitted "subsequently" with the timeline remaining unclear. **Proposed change (if any):** Keep the wording of section 4.3.2.4 of the current guideline (October 2005)	

Please feel free to add more rows if needed.