SUBMISSION OF COMMENTS ON THE
Detailed guidance for the request for authorization 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.

Daft Revision 3, […] 2009

COMMENTS FROM F. Hoffmann-La Roche Ltd.

1. GENERAL COMMENTS

Organisation	General Comment	Response from EMEA/EC [*to be completed by EMEA/EC*]
F. Hoffmann-La Roche, Basel Comments consolidated by Surendra Gokhale/Team	We miss any reference/comments on protocol deviations/violations in the document. How should these be managed and what are the applicable criteria for reporting? Of general concern is the fact that in the some Member States, certain forms are still to be submitted in local language. This generates a workload which may be unnecessary, has the potential to introduce inconsistency and may, indirectly, slow down overall integration and harmonization processes.	

2. SPECIFIC COMMENTS ON TEXT

Line No +[1] Paragraph No Page No	Organi-sation	Comment, Rationale and Proposed Changes *If changes to the wording are suggested, they should be highlighted*	Response from EMEA/EC [*to be completed by EMEA/EC*]

[1] Where available

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Page 4, section 1.1. , 2nd paragraph.	**F. Hoffmann-La Roche, Basel**	**Comments:** This paragraph states that member states are not allowed to add on Community rules but it is not clear to what extent the content is mandatory to be followed by all MS, as last paragraph of section 1.1 on page 5 says MS shall consider this guidance. A **clearer statement** is needed in order for the process to become truly standardized in all MS and local deviations can be avoided in the future. In addition, avoidance of discrepancies between different local interpretations of the same requirement needs to be addressed in the document.	
Page 7, section 2.1.1., 2nd paragraph		**Comments:** Please clarify the term *inasmuch which is already part of* Article 9(1), 2nd sub-paragraph and (2) of Directive 2001/20/EC. We suggest to substitute or explain the language used in this article of the Directive.	
Page 7, section 2.1.2 2nd paragraph		**Comments:** It is stated that the validation of the request for authorization forms part of the 60 day approval period. Please reconfirm as MS have additional validation periods (10-15 days) on top of the 60 days. This should be clear so the MS do not make their interpretation of this requirement. 2nd paragraph last sentence: If the request is not valid, what happens procedurally? Will this also apply to ECs? Please clarify.	
Page 8, section 2.1.4.3., 2nd paragraph first sentence		**Comments:** Use of the word *"letter"* twice for different things is confusing. ….and use a resubmission "*code letter*" instead of just "*letter*". This would be clearer to the reader.	
Page 8, section 2.1.4.3, line 8		**Proposed change (if any):**	

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		From the sentence: "*The initial contact should be by telephone and, for reasons of traceability, by fax or email*" …… we propose to remove the part of the sentence: " telephone and, for reasons of traceability")	
Page 9, section 2.1.6		**Comments:** Could it be made mandatory to accept documentation in English for multinational trials (except that for tax payments and for patient related documentation). As the legislation is international, HA should understand English as well as EC, who should follow the global legislation.	
Page 9, section 2.2. (c)		**Proposed Change**: Unless the protocol allows other alternatives, it should be ensured IMP and NIMPs are the same for all MS participating in the trial, except if NIMPs are not marketed in a given MS.	
Top of page 10, section 2.2., *"Covering Letter"*		**Comments:** If the trial is part of an **approved/valid** PIP… (otherwise, the decision would not be available yet). **Proposed change (if any):** If the clinical trial is part of an approved/valid Paediatrics Investigation Plan ("PIP") as referred to in Chapter 3 of Regulation ….(indicate status of the PIP in the cover letter).	
Page 10, Section 2.4.		**Comments:** Application Form: An explanation of what is considered a "*sub-study"* could be included. A global/uniform definition of a *sub-study* would avoid different interpretations and ways of submission for a same sub-study associated to a protocol in the participant countries	
Page 11, section		**Comments:** Please specify which kind of disk should be used.	

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2.4., line 11		Proposed change: To add the term "compact" **N.B.:** Not in all the countries, the XML file is attached on a disk (e.g. in Spain, a telemetric system is in place). In this particular case, the signature is an electronic certificate.	
Top paragraph on page 12, section 2.5.		**Comments:** Both, number and date, to identify the protocol version should not be mandatory as it could be identified by letters.	
Page 13, section 2.5		**Comments:** It appears that one situation which is fairly common during the EIH stage was missing, i.e. for those mechanism related AEs, sponsor should provide possible medical rescue procedure/therapy in the protocol to help the PI in dealing with the situation. **Proposed change (if any):** Adding one additional statement to make the point made above a requirement	
Page 13, section 2.5, line 1 Line 3 Line 6		**Proposed change (if any):** Replace"*doses"* with *"dosing of individual subjects"* Add a bullet point *"Dose de-escalation scheme"* Add bullet point *Prohibited coexistent medication*	
Page 13, Section 2.6., "IB", 4th Para		**Comments:** …. ("SmPC") may replace IB if the IMP is authorised in any Member State or ICH country. Is the local PI from ICH country acceptable for replacement for SmPC? The	

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		document would benefit from confirmation and /or clarification of this item.	
Page 13, IB section 2.6., line 5		**Proposed change (if any):** Add the word "*trial*" in sentence: A request for *trial* authorisation has to be accompanied with an IB.	
Page 14, section 2.7., 5th paragraph		**Comments:** The following statement is not clear: "The dossier should not generally be a large document, however for trials with certain types of IMPs exceptions can be agreed with the member state concerned". Proposed change (if any): Please clarify what types of trials and what exceptions should be agreed with MS. Specify number of maximum pages for the "standard" dossier.	
Page 15, section 2.7.1., last part of second bullet point		**Comments:** "Typo" in the sentence: "certification of the **CMP** compliance of the manufacturing of any active biological substance" **Proposed change (if any):** "certification of the **GMP** compliance of the manufacturing of any active biological substance"	
Page 17, Line 1 and 2, section 2.7.3.		**Comments:** What if clinical events are observed/reported from a non-GCP trial? **Proposed change (if any):** It might be helpful to add the following fragment in front of this item: "All relevant clinical safety information should be summarized in the Previous Human Experience section. For studies conducted in accordance with the principles of GCP, the applicant should supply the following:…"	

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Page 17, section 2.7.3. 1st bullet point		**Comments:** Please clarify what is meant by "GCP status".	
Page 17, section 2.7.4, 3rd paragraph, line 8		**Comments:** An increasing number of clinical studies appear to suggest that the trough plasma concentration (Cmin) may be more relevant for the efficacy of a drug candidate. **Proposed change (if any):** The wording for the item could be: "…preferably based on the parameters indicative of the rate and extent of drug exposure in plasma such as AUC, Cmax, or Cmin, whichever is considered most clinically relevant, rather than in terms of applied dose"	
Page 18, 2.8.2.,		**Comments:** It is mentioned that cross reference is permitted when IMP related information is contained in another CTA to national CA. However, in the Netherlands, the CA gives only formal approval as EC performs the actual assessment. The responsible EC varies for every trial. So the question arises if and how different ECs can manage this cross referenced information? Explanation is needed in this context.	
Page 18 Section 2.8.3., Title		**Comments:** "Typo" in the title: "Possibility to refer to the Possibility to refer to the SmPC **Proposed change (if any):** Possibility to refer to the SmPC	
Page 23, section 3.3.1.		**Proposed change (if any):** Add to in Title: Amendments as regards **to** the clinical trials protocol	

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Page 23, section 3.3.1. 1st bullet point 2nd bullet point 5th bullet point		**Comments :** Add Reducing *or increasing* the number of clinic visits Please clarify what it is mean by the term "monitoring procedure": Does this apply to "the monitor" or patients related procedures/monitoring of e.g. physical functions? Does a change of monitor represent a substantial change? Add Change in dose - increase or decrease	
Page 23, section 3.3.1. 2nd Bullet point		**Comments :** Bullet point number 5 seems to be also partially included in bullet point number 2. **Proposed change:** To delete bullet point 5 and merge the information.	
Page 23, section 3.3.1. 7th bullet point		**Comments :** Under non substantial, [Bullet point 1] – it is not clear what changes in the recruitment procedure are still minor (examples would help).	
Page 25, section 3.4., paragraph 4		**Comments:** In some countries, it does not apply/is not possible to attach a copy of the decision to the Substantial Amendment Form. **Proposed change (if any):** Please consider adding: "if applicable". "To provide this information it will be sufficient to submit the Substantial Amendment Form once the decision on the substantial amendment has taken place, indicating in Section A.4 that it is "for information only", and attaching a copy of the decision **(if applicable)"**	
Page 26, section 3.5. (c), 2nd Bullet point		**Comments:** In all cases, when changes are made to the document, they should be identified with updated version and date and not only when the changes are widespread or far-reaching?	

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		Is this correct? Please clarify? **Proposed change of text for last sentence of second bullet: "**In this case, an additional table should summarise [instead of list] the amendments to the documents. List could still be interpreted as a requirement to comprehensively point out any difference, which is not feasible in cases where the structure of a document has been thoroughly changed. It's more reviewer friendly to highlight the relevant changes in a summary table. –	
Page 27, section 3.5. (f)		**Comments:** The revised copy of the XML should be always submitted even if just new sites or PI changes? Can this be clarified? **Proposed change:** **To add: <u>except in cases of site/PI changes, when the updated file is not mandatory to be submitted</u>**.	
Page 27, section 3.5. (f)		**Comments:** Not in all the countries, the XML file is attached in a paper document (e.g. in Spain, there is a telematic system in place). **Proposed change:** To delete "a print out of the" and leaving: "by attaching a revised form…"	
Page 27, Section 3.6. 4th paragraph		**Comments:** Is there a validation period defined for amendments?	
Page 30 section 3.10., top of page, 2nd		**Comments:** It is mentioned that "*the sponsor should immediately implement the course of action"*, but this could also be an investigator or any other person involved in the	

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paragraph		trial as defined in the 1st paragraph of this section. **Proposed change:** To modify that sentence: "*the sponsor or the investigator* ***or any other person involved in the conduct of the trial*** *should immediately implement the course of action"*	
Page 31 section 4.2.1. 2nd paragraph		**Proposed change:** To add: Both, notifications on a local and global level, could be combined in the same notification - if they occur within the 90 days period.	
Page 31, section 4.3.		**Comments:** There are not timelines given for submission of clinical trial summary after notification of end of the clinical trial. **Proposed change (if any):** However, the clinical trial summary report can be submitted subsequently to the end of trials notification (**but needs to be submitted within 12 months of the end of the trial**).	
Page 31 section 4.4		**Proposed change:** It could be useful to include some examples of follow up info that CAs and ECs should be notified of.	