SUBMISSION OF COMMENTS ON: draft revision 3 of 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
COMMENTS FROM: BPI – German Pharmaceutical Industry Association, Germany
GENERAL COMMENTS: BPI would like to thank the European Commission for the opportunity to comment on the proposed guideline.
7. September 2009

	Section text	Comment
General	The previous guideline contained as appendix 1 a table of requirements for each Member State. This has been deleted.	Although there is a document "CTA assessment in member states" issued by the CTFG this document is less complete as it does not include general info (such as language requirements) We, therefore, propose either to include the Table of requirements of MS again in the revised CT1-guidance or to urgently advise the CTFG to amend their document.
2.1.2.	In accordance with Article 9(4) of Directive 2001/20/EC, consideration of a valid request for authorisation by the national competent authority shall be carried out as rapidly as possibly and may not exceed 60 days, subject to exceptions set out in this Article. Validation of the request for authorization forms part of the delay of 60 days. Day 0 is the day of submission of the request. If the request is valid, on day 60 at the latest the consideration of the request has to be finalized.	This is unfortunately not true in all countries, i. e. 2001/20/EC but it often overridden by local legislature. For example, in CZ, the law stipulates that 10 days maximum can be taken for validation of the dossier plus 60 days for review. What exactly is meant by 'request has to be finalized' – Does it mean that the the approval letter has to be issued on day 60 the latest?
2.1.4.1.	Application is not valid If an application is not valid the national competent authority will inform the applicant and give the reasons.	
2.1.4.2.	Amendments during the authorisation phase Following the submission of a request for authorisation, the sponsor may want to submit changes to the documentation. This may happen either: • Following notification of grounds for non-acceptance by	This requires that if an applicant submits amendments during review of the CTA, by its own initiative, the review clock will be restarted. It is appreciated that this is intended to prevent applicants from making early submissions, with the knowledge that a revision, perhaps to a protocol, is about to be made, in order that the review clock commences. While it is understood that such action warrants additional review time for the competent authority CA), it would be more reasonable to add a further 35 days to the original review clock rather than re-starting it. This would

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	the national competent authority of the Member State concerned: In this case Article 9(3) of Directive 2001/20/EC applies; or • At the initiative of the sponsor, for example following the opinion of the Ethics Committee or in view of new relevant safety information: In this case, the timeframe set out in Article 9(4) of Directive 2001/20/EC re-starts, i.e. the amended request for authorisation shall be considered as rapidly as possible and may not exceed 60 days.	the same as if the amendment was submitted after the CTA was approved, but would minimise the administrative aspects of separate approvals for the initial and amended applications respectively. What exactly is meant with 'new relevant safety information' that justifies an amendment during the authorization phase.. Frequently, SUKL disagrees with the sponsor's assessment of the safety-relatedness. It is often debated that 'new safety information' no matter at which stage of the trial it occurs, requires a fee payment
2.4.	Applicant signature	It is proposed that clarification should be given that applicants who are neither sponsor nor legal representative of sponsor are not personally responsible for any statements when signing the application form. This clarification may be given either in the revised CT1-guidance or in the information for guidance on completing the EudraCT application form.
2.7.1.	Quality data If the IMP does not have a marketing authorisation and is not manufactured in the EU	It should be clarified whether this refers to an authorisation in the EU (as in the bullet point above) or to any authorization globally.
2.7.3.	*Previous clinical trial and human experience data* • in case the clinical trials referred to has been performed in third countries, a reference to the entry of this clinical trial in a public register, if available. In case a clinical trial is not published in a register, this should be explained and justified.	It is unclear why the absence of a study in a public register needs to be justified. Inclusion of studies in public registers is usually not a regulatory requirement. It is mostly optional and is undertaken in order to facilitate publication of study results in key journals.
2.8.	*Simplified IMPD* The sponsor has the possibility to submit a simplified IMPD if the information can be made available by referring to other submissions. This is the case if: • the information related to the IMP is contained in the IB; • the information related to the IMP is contained in another clinical trial application to the national competent authority of	The word "or" should be inserted after the first bullet point.

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	the Member State concerned and has been assessed previously; or • τhe information related to the IMP is contained in the SmPC and has been assessed previously as part of a marketing authorisation in any Member State or in an ICH country.	
2.8.3.	*Possibility to refer to the SmPC* The sponsor may submit the current version of the SmPC as the IMPD if an IMP has a marketing authorisation in any Member State or in an ICH country and is being used in the same form, for the same indications and with a dosing regimen covered by the SmPC.	It should be clarified that throughout this section, reference to the SmPC includes the equivalent documentation in the relevant ICH country, such as US physician's information."
2.9.	Non-investigational medicinal products used in the trial Where NIMPs without a marketing authorisation in the EU are used, or used outside the conditions of a marketing authorisation, a NIMP dossier may be requested by the competent authority of the Member State concerned on a case-by-case basis if this is necessary in order to fully assess the safety of the clinical trial.	Add: Where a NIMP used does not have a marketing authorisation in the EU but is authorised in an ICH country, it is recommended that the relevant equivalent of the SmPC be submitted. If the product is used outside the terms of its approval, a NIMP dossier may be requested by the competent authority of the Member State concerned on a case-by-case basis if this is necessary in order to fully assess the safety of the clinical trial." See also proposal of the CTFG
2.10.	2.10. Other documents to be submitted The following additional documents should be submitted as attachment to the covering letter:	It is proposed to complete this list e.g. copy of the label, facilities and finance related information.
	The IMP is a placebo and the placebo has the same composition, is manufactured by the same manufacturer and is not sterile	The sentence should read: The IMP is a placebo and the placebo has the same quantitative composition with regards to excipients, is manufactured ,,,
3.1.	Legal basis and scope Notification/submission for information[40] is only obligatory if the amendment is substantial or otherwise significant. 40 Directive 2001/20/EC distinguishes between *notification* of the national competent authority and *information* of the Ethics committee. For the purpose of this guideline,	The guideline distinguishes between notification to CAs and submission to Ethics Committees (ECs), consistent with Directive 2001/20/EC. While this is reasonable, it would also be beneficial if the guideline clarifies that the substantial amendment form is intended to be (although it is not) consistent with this. The form states: • A.2 Notification for authorisation to the competent authority: and • A.3 Notification for an opinion to the EC:

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	both submissions shall be referred to as “notification”.	
		In addition, it is suggested that the phrase “for information” be deleted. This implies that no action on the part of the recipient is required, where in fact review is required within 35 days by the EC (per the legislation) and by the CA (per the guideline). In fact there are circumstances where non-substantial amendments are submitted for information only. This occurs where a regulatory authority is informed about a substantial amendment relating to information previously assessed by the EC but not by the RA (and vice versa)
3.2.	The notion of “amendment” Substantial amendments as referred to in Article 10(a) of Directive 2001/20/EC are only those which are introduced after approval of the clinical trial by the national competent authority or the Ethics Committee respectively. This means that the following is not an “amendment”:	Section 3.2. is intended to address the definition of an amendment while Section 3.3. is intended to address the definition of substantial amendment. However Section 3.2 actually commences by defining a substantial amendment (which has a legal definition), not an amendment (which does not have a legal definition.)
3.2.	The notion of “amendment” Changes of the contact details of the sponsor (e.g. a change of email or postal address) are not considered as amendment, if the sponsor remains identical.	This does appear to constitute an amendment however it is not substantial. This text should be moved to the following section: “3.3.3. Amendments as regards other initial scientific documents supporting the Request for authorisation of the clinical trial - Non-substantial”
3.3.1.	Amendments as regards the clinical trials protocol	Although a list of non-substantial amendments is now included, the list of substantial amendments is the same as in the current guideline. It would be helpful to extend this list considerably, in particular to changes which are less obviously substantial.
3.3.1.	Amendments as regards the clinical trials protocol Non-substantial Change in the documentation used by the research team for recording study data (e.g. in the case report form);	This example can be interpreted in different ways and should be clarified.

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3.3.1.	Amendments as regards the clinical trials protocol - Non-substantial: Limited lengthening of the trial time.	This is a subjective statement which will of course depend on the originally planned study duration. However, examples of what might be considered "limited" would be helpful.
3.3.2.	Amendments as regards the Investigational Medicinal Products Dossier - Non-substantial: Minor changes in the labelling of the investigational product;	Examples of what constitutes "minor" would be helpful.
3.3.3	Amendments as regards other initial scientific documents supporting the Request for authorisation of the clinical trial In addition, concerning changes to the IMPD, reference is made to Chapter 8 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.	This should be moved to the end of the section: "3.3.2 Amendments as regards the Investigational Medicinal Products Dossier"
	Changes of internal organization of the sponsor or of the person to which certain tasks have been delegated	This requires clarification as it is unclear what types of organisational changes would be included as an amendment, whether substantial or otherwise.
3.6.	Time for response, implementation	It would be helpful to agree a common validation period for substantial amendments, across the EU.
3.7.	*Ex post* notification of urgent safety measures	This is a sub-section of Section 3 "Amendments", however, not all urgent safety measures are amendments. The mentioned DMC halting a study seems to be an early termination. as this section refers to temporary halts different from a DMC halt.
3.9	Temporary halt of a trial	This is a sub-section of Section 3., however, not all temporary halts are amendments, as outlined in the guidance, so their management should be addressed in a sparate section.
3.9.	Suspension/prohibition of a clinical trial by the national competent authority in case of doubts about safety or scientific validity	This is a sub-section of Section 3., however, these are not amendments so their management should be addressed in a separate section.
3.10.	Non-compliance with the applicable rules on clinical trials	This is a sub-section of Section 3., however, these are not amendments so their management should be addressed in a separate section.
4.3.	Clinical trial summary report The clinical trial summary report is	The timeline for submission should be included. The previous guidance stated that the summary may be submitted within one year.

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	part of the end of trials notification. However, the clinical trial summary report can be submitted subsequently to the end of trials notification.	