The European Association for Bioindustries

SUBMISSION OF COMMENTS ON "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)"

COMMENTS FROM EUROPABIO

GENERAL COMMENTS

EuropaBio welcomes the opportunity to input into the European Commission consultation on the proposed revision of the 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.

Overall EuropaBio welcomes and supports the revision of the guidance which provides helpful clarifications and the possibility of cross-referencing between documents. Moreover the inclusion of illustrative examples to provide practical guidance regarding substantial amendments is particularly helpful.

EuropaBio believes that this guideline is a step in the right direction towards harmonization of the requirements for clinical trial applications between EU Member States.

We note that the draft revised guidance does no longer include Attachment 1 which summarises the national requirements and specific information required by each EU Member State for clinical trial applications. Whilst we understand the rationale for the deletion of the Member State specific information, we would like to point out that it is important that the revised guidance expressly states that this information has been removed and indicates if this information would be relocated to the Heads of Medicines Agencies website, as otherwise applicants will believe that they no longer need to comply with the additional national requirements. Member companies have reported that such an up-to-date-list of national requirements, be it attached or available online, is very useful when gathering documentation and preparing clinical trial applications for submission to each national competent authority.

We welcome the opportunity to submit these observations and comments and hope they are helpful in improving this guidance with greater clarity. We believe that the detailed guidance for clinical trial applications is important in establishing clear expectations of the data requirements for both applicants and national competent authorities in the EU.

Comments on **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**

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
1.1 Page 4	Clarification is requested regarding the following statement: "In this respect, Directive 2001/20/EC is exhaustive, i.e. the harmonisation is not based on minimum requirements, and Member States are not allowed to "add on" the community rules." We understand that the contents and format of the clinical trial application are as described in the guidance and that this is to be accepted by all national competent authorities in the EU. If this is the case, this will greatly reduce administrative burden in applying for clinical trial authorisations with optimal use of limited resources for other key activities. However, some Member State national competent authorities have imposed different national requirements, some of which go beyond those set out in the Clinical Trials Directive and the guidance. Therefore we would expect the national competent authorities to revise their requirements in accordance with the guidance once finalised and adopted by the Ad hoc group for the development of implementing guidelines for the Clinical Trials Directive.	
2.1.2 Page 7	It is stated that the validation of the request for authorisation thus forms part of the delay of 60 days, and 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 finalised. We would suggest that this is revised to include the following points: - the validation period (time between the reception of the request by the national competent authority and the validation acknowledgment) - the possibility of an extended evaluation period (up to 90 days) for certain products as per Article 9(4) of Directive 2001/20/EC.	"Day 0 is the day of **receipt** of the request. **In all cases, day 0 will be the date when the request will be considered as valid by the national competent authority**. If the request is valid, on day 60 at the latest (**or day 90 for certain types of products referred to in Article 9(4) of Directive 2001/20/EC)**, the consideration of the request has to be finalised".

Comments on **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**

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
2.1.4.2 Page 8	Changes to the documentation at the initiative of the sponsor following receipt of the opinion of the ethics committee should not lead to another 60-90 days assessment, unless new important safety information requires amending the clinical trial protocol in which case an extension could be warranted.	
2.1.6 Page 9	The draft revised guidance does not refer to any documents that are specifically required to be in the local language, therefore a common language, English, should be accepted by all national competent authorities.	Delete this section.
2.3 Page 10	"Before submitting an application to the national competent authority, the sponsor should obtain a unique EudraCT number from the EudraCT database by the procedure (…)" We propose to add "or any of its delegates" after "sponsor" for further clarity and consistency with regards to obtaining the EudraCT number.	"Before submitting an application to the national competent authority, the sponsor **(or its appointed representative)** should obtain a unique EudraCT number from the EudraCT database by the procedure (…)"
2.4 Page 11	It is stated that certain information contained in the application form is going to be made public. It would be helpful to have additional guidance as regards publication, such as data entry convention (e.g. English vs. other EU languages, scientific vs. layman).	
2.5 Page 11	It would be helpful to know as to whether the Community guideline (CPMP/ICH/135/95) will be updated to ensure alignment with the requirements of Directive 2001/20/EC.	
2.5 Page 12	Some Member State competent authorities have requested a signature from a co-ordinating investigator in every country where the trial is taking place to be submitted to each member state. We suggest amending paragraph 1 to improve clarity on this point.	**"**……..be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials) **in the Member State concerned**."
2.6 Page 13	Paragraph 3 should refer to Directive **2005/**28/EC.	

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
2.7 Page 14	It is stated that the IMPD 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. Clarification is sought on the wording "certain types of IMPs" and what is meant by "large document", i.e. no more than X pages. Moreover we would welcome additional practical guidance for discussing these exceptions.	
2.7.1 Page 15	We would suggest clarifying that viral safety data should be provided for biotechnology IMPs, while this information should not be required for non modified comparator products marketed in the EU or ICH region and administered according to the instructions provided in the SmPC.	
2.7.1 Page 15	Certification of the "CMP" compliance of the manufacturing of any active biological substance" should be corrected to "**GMP"**.	
2.7.2 Page 16	It is stated in the section relating to non-clinical pharmacology and toxicology data that all studies should meet the requirements of GLP guidelines where appropriate. Reference to the relevant guidelines should be added after "where appropriate".	
2.7.3 Page 17	We fully support this important initiative for improving the transparency of clinical trials conducted by sponsors in all geographic regions. However, it is inappropriate to request information on clinical trial registry disclosures for trials in third countries in the technical application dossier because this is not a criterion for the evaluation of the clinical trial application.	Delete the second bullet point.
2.7.4 Page 17	With regards to the overall risk and benefit assessment, it is stated that: "This section should provide a brief integrated summary that	"This section should provide a brief integrated summary that provides a critique of the non-clinical and clinical data and their relevance to the potential risks and benefits of the proposed trial, **unless this information**

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
	critically analyses the non-clinical and clinical data in relation to the potential risks and benefits of the proposed trial." Since this information is of utmost importance for the investigators, it would be appropriate to make it available in the protocol. Consequently, the sponsor should be allowed to cross-refer to the protocol.	**is already provided in the protocol. In the latter case, the sponsor may cross-refer to the relevant section of the protocol**."
2.8 Page 17	We would suggest making reference to Table 1.	"The Sponsor has the possibility to submit a simplified IMPD if the information can be made available by referring to other relevant submissions **(see Table 1)**"
2.8.2 Page 18	With regards to the possibility to refer to an IMPD which was submitted previously, it is stated that: "This may require a letter from the other applicant to authorise the national competent authority to cross-refer to their data." We would welcome further guidance on the cases where the letter from the other applicant may or may not be required.	
2.8.3 Page 19	We would suggest defining ATC the first time this term is introduced.	"In those situations, provided that the IMP is not modified e.g. overencapsulated, it is acceptable that IMPs to be used are only identified by the active substance name or ATC **(Anatomic, Therapeutic, Chemical)** code as follows (…)"

<table>
<tr><th colspan="3">SPECIFIC COMMENTS ON TEXT</th></tr>
<tr><th>Section No.
& Page No.</th><th>Comment and Rationale</th><th>Proposed change (if applicable)</th></tr>
<tr><td>2.8.5
Page 20</td><td>We would suggest adding “or ICH country” after “EU Member State” to ensure consistency.</td><td>
<table>
<tr><td>Types of Previous Assessment</td><td>(…)</td></tr>
<tr><td>The IMP has a MA in any EU Member State or ICH country and is used in the trial without any modification of the IMP: _ Within the conditions of the SmPC _ Outside the conditions of the SmPC _ After it has been blinded</td><td>(…)</td></tr>
<tr><td>Another pharmaceutical form or strength of the IMP has a MA in any EU Member State or ICH country and the IMP is supplied by the MAH</td><td>(…)</td></tr>
<tr><td>The IMP has no MA in any EU Member State or ICH country but drug substance is part of a medicinal product with a marketing authorisation in a MS and: _ is supplied from the same manufacturer _ is supplied from another manufacturer</td><td>(…)</td></tr>
</table>
</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th colspan="3">SPECIFIC COMMENTS ON TEXT</th></tr>
<tr><th>Section No.
& Page No.</th><th>Comment and Rationale</th><th>Proposed change (if applicable)</th></tr>
<tr><td>2.8.5
Page 20</td><td>With regards to “Outside the conditions of the SmPC” in Table 1 (first row) it is proposed to make reference to the drug product data (P) and the appendices of the IMPD (A) in the “Quality Data column”, especially where the condition of use or assembly (formulation or packaging) are outside the conditions of the SmPC.</td><td>
<table>
<tr><th>Types of Previous Assessment</th><th>Quality Data</th><th>(…)</th></tr>
<tr><td>The IMP has a MA in any EU Member State or ICH country and is used in the trial without any modification of the IMP:
_ Within the conditions of the SmPC
_ Outside the conditions of the SmPC
_ After it has been blinded</td><td>SmPC
SmPC (and P+A if appropriate)
P+A</td><td>(…)</td></tr>
</table>
</td></tr>
<tr><td>2.9
Page 21</td><td>With regards to non-investigational medicinal products used in the trial, the guideline implies that in some circumstances a NIMP dossier may or may not be requested by national competent authorities for a clinical trial application. This encourages a non-harmonised approach.</td><td>“Where NIMPs without a marketing authorisation in the EU are used, or used outside the conditions of a marketing authorisation, the applicant should provide sufficient information on the NIMP to allow the assessment of the safety of the clinical trial.”</td></tr>
<tr><td>3.1
Page 21</td><td>We would suggest that the guidance clarifies the following points.

It is implied in Article 10(a) of Directive 2001/20/EC that the sponsor makes the decision as to whether an amendment to a clinical trial meets the criteria of a substantial amendment requiring notification or not.

Moreover, sponsors frequently receive requests from national competent authorities to be immediately notified / informed of non-substantial changes. This appears to be contradictory to the recommendations in the guidance (October 2005):</td><td>“The sponsor is required to make a decision on whether an amendment to a clinical trial is substantial. Notification/submission for information is only obligatory if the amendment is substantial or otherwise significant. Directive 2001/20/EC does not require notification or immediate submission for information of non-substantial amendments.

As a general rule, such changes should instead be recorded and if appropriate included in the next update of the trial documentation and be available on request for inspection at the trial site and/or the sponsor’s premises as appropriate. ”</td></tr>
</table>

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
	"However, they should be recorded and if appropriate included in the next update of the IB and be available on request for inspection at the trial site and/or the sponsor's premises as appropriate".	
3.2 Page 22	The revised guidance clarifies that changes of the contact details of the sponsor (e.g. change of email or postal address) are not considered as amendment, provided the sponsor remains the same. It is stated that this information should be transmitted to the national competent authority of the Member State concerned as soon as possible. Clarification is requested as to whether changing the contact person of the sponsor or the EU legal representative is considered an amendment. It should be noted that a change of contact details implies a change to the EudraCT XML file. Member companies expressed concerns that some national competent authorities currently regard any change to the XML file as a substantial amendment by default.	
3.4 Page 25	The revised guidance provides a few examples clarifying the assessment responsibility between the competent authority and the ethics committee. However the primary responsibility is in many other instances much less clear, giving the impression that 'overlapping' assessments may be a growing issue and sometimes resulting in conflicting outcomes. Therefore it would be helpful if the guidance clearly sets out the expectations and the assessment responsibility for each body as regards substantial amendments. Additionally paragraph 3 states: "It is recommended that the respective other body is informed about the substantial amendment. 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	"It is recommended that the respective other body is informed about the substantial amendment. 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

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
	Section A.4 that it is "for information only", and attaching a copy of the decision." We would suggest including a sentence for added clarity.	"for information only", and attaching a copy of the decision. **A copy of the opinion of the Ethics Committee of the Member State concerned should be provided once available, whether the request for substantial amendment has been submitted in parallel or sequentially, unless the Ethics Committee informs the sponsor that is has copied its opinion to the national competent authority."**
3.5(f) Page 27	It is stated that a printout of the revised EudraCT form showing the amended fields highlighted should be submitted. However the current Amendment Notification Form (published in Volume 10 of EudraLex) requires a "copy of the initial application form with amended data highlighted", while Annex 2 (Substantial Amendment form) states a "revised .xml file and copy of the initial application form with amended data highlighted". It would be helpful if the Substantial Amendment Form is updated to ensure consistency.	
3.8 Page 28	It would be helpful if the section relating to temporary halt of a trial differentiates between: - a temporary halt to all aspects of the trial (enrolment/recruitment and treatment of patients on study drug); and - a temporary halt as regards enrolment of new patients into the study (but where patients already enrolled in the study continue to receive the IMP as per the protocol). This section of the guidance is very much focused on safety driven trial halts, which would always fall under the 'significant/substantial' or 'urgent safety measure' umbrella. However, a sponsor may wish to temporarily halt enrolment of new patients into a study (while those already on study continue to receive IMP(s) as per the protocol) for other non-safety/non-substantial reasons; e.g. during	

SPECIFIC COMMENTS ON TEXT		
Section No. & Page No.	**Comment and Rationale**	**Proposed change (if applicable)**
	discussions on future study design modifications. In this scenario one could argue that although the future amendment to the protocol/design would be a substantial amendment, the actual temporary halt to enrolment is non-substantial.	
3.11 Page 30	It is stated that non-substantial amendments should be recorded and if appropriate included in the next update of relevant documents. We would suggest revising this statement for added clarity.	"(…) However, non-substantial amendments should be recorded and if appropriate included in the next update of the relevant document, **i.e. in the submission of a subsequent substantial amendment or in the clinical study report,** and be available (…)"
4.3 Page 31	A timeline for submission of the clinical trial summary report would be welcomed.	