8th September 2009

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

COMMENTS FROM:

Name of Organisation or individual
European Federation of Pharmaceutical Industries and Associations – EFPIA

1. GENERAL COMMENTS

Stakeholder No.	General Comment	Outcome (if applicable)
	This revision to the guideline has provided general improvements through cross-referencing of other guidelines and legislation and the inclusion of examples. **1. National requirements** We have noticed the deletion of the list on specific information required by MS for applications to a Competent Authority, corresponding to Attachment 1 of the previous guidance. While we would appreciate a complete harmonisation of Clinical Trial Applications requirements within the EU, some Member States still have specific requirements. While harmonisation of requirements is not completely fulfilled, it might be helpful to publish the list of Member States requirements, for example on the HMA Clinical Trials Facilitation Group Webpage. **2. Procedures** The revised guideline unambiguously states that the 60-day review period starts at the time of a valid request is received and that, consequently, the validation step is integral part of the 60 day period. This clarification is welcomed by EFPIA. A few MSs regularly exceed the 60-day time limit. Conflicting interpretations on how exactly the 60 day limit should be applied are also in use. We hope that the clarification will translate into a better harmonisation between MSs, increased transparency and improved predictability for sponsors. **3. Substantial amendments**	

Stakeholder No.	General Comment	Outcome (if applicable)
	EFPIA welcomes the removal of the previous Attachment 5, which did little to clarify whether an amendment is substantial or not, and the inclusion of examples of changes that would typically be considered as non-substantial amendments. In view of the experience with the clinical trials directive rather more examples of changes that would **categorically** be regarded as non-substantial would have been expected and useful **4. Transparency** Regarding the transparency of clinical trials conducted by sponsors in all geographic regions, we fully support the importance of this initiative. However, it is inappropriate that the revised guideline includes a requirement for information on clinical trial registry disclosures for trials in 3rd countries in the technical dossier of application. The fact of disclosure or non-disclosure of 3rd country trials in public registries must not be a criterion for the evaluation of the application. **5. IMPD** EFPIA welcomes that reduced information will be allowed for IMP with a MA in any ICH country. In line with guidance CHMP/QWP/185401/2004 final we also suggest to extend this to IMPs with a MA in a MRA partner.	
	The English content of the guideline needs to be improved.	

2. SPECIFIC COMMENTS ON TEXT

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
Section 1.1 Paragraph 2 p. 4/37		**Comments:** EFPIA welcomes the Commission's emphasis that the aim of the Directive is harmonization of the rules in the Community relating to clinical trial authorizations and in particular, the explicit statements that the requirements set out in the Directive are exhaustive and Member States may not therefore "add" to the Community rules. Given the clear position set out in the guidance together with the fact that the table of Member States' requirements has been removed, EFPIA assumes that Member States have agreed they will no longer require applicants to provide information pursuant to national requirements (save for translations) if that information is above and beyond that mandated by the Directive. EFPIA recognizes that it may be necessary for some Member States to amend their national rules in order to be able to comply with this aspect of the guidance and that this will take time. Until all such amendments have been made, the guidance should reference or provide a link to where applicants may find the list of national requirements (e.g. Clinical Trials Facilitation Group section of Heads of Medicines Agencies website)	
Section 1.2 Paragraph 1 p. 5/37		**Comments:** The list of concerned products has been simplified. 'Biotechnological products', 'cell therapy products' and 'gene therapy products' have been removed from the list, although the latter two are now included in 'ATMPs'. 'Chemical entities' and 'other extractive products' have also been removed from the list. Even if the list does not pretend to be comprehensive ("includes interventional clinical trials involving:..."), and even if it is quite obvious that this guidance apply to these products as well (same scope as the Directive 2001/20/EC involving all medicinal products defined in Article 1(2) of Directive 2001/83/EC), it would be clearer to maintain these categories of products in the list.	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		A suggestion could be to mention only products out of scope, with everything else automatically being within scope.	
Section 2.1.2 Paragraph 3 p. 7/37		**Comments:** The revised guideline unambiguously states that the 60-day review period starts at the time of a valid request is received and that, consequently, the validation step is integral part of the 60 day period. This clarification is welcomed by EFPIA. A few MSs regularly exceed the 60-day time limit. Conflicting interpretations on how exactly the 60 day limit should be applied are also in use. We hope that the clarification will translate into a better harmonisation between MSs, increased transparency and improved predictability for sponsors.	
Section 2.1.4.2 Bullet 2 p. 8/37		**Comments:** Consideration should be given to the significance of the information and the amount of documentation before the review clock of 60 days is restarted. For minor changes, the review should be finalised in the originally assigned timeline and only new data and modifications of the protocol should be additionally evaluated during the ongoing process. For completeness, it should also be added that changes might also be requested by CAs of other concerned countries in case of multinational trials. **Proposed change:** - at the initiative of the sponsor, for example following the opinion of the EC **or a another Competent Authority** or in view of new relevant safety information. **In case of substantial changes requiring a re-assessment of the application,** the timeframe re-starts, i.e. the updated request for authorisation shall be considered as rapidly as possible and may not exceed 60 days.	
2.1.4.3 Withdrawals		**Comments:** The person submitting the request for authorisation (the “applicant”) may not be the sponsor or legal representative, but could be a person authorised by the	

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		sponsor to act on their behalf. As such, the applicant must also be permitted to withdraw the application. **Proposed change:** "The sponsor or his legal representative or the applicant should inform the national competent authority…"	
Section 2.1.6 p. 9/37		**Comments:** We would like to suggest the use of a single language for CTA submissions. The use of English would seem appropriate similarly to what is done with MAA submissions. This would of course not apply to documents that are directed to the subjects/patients and site/hospital staff involved in the study. For these documents, it would be appreciated if language requirements could be specified in tabulated form within this guidance or on a dedicated information source (e.g. the CTFG homepage).	
Section 2.2 Paragraph 6 p. 10/37		**Comments:** Proposal to change the wording for clarification. Only for approved / valid PIPs, decisions are available. **Proposed change:** 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).	
Section 2.3 p. 10/37		**Comments:** The guidance does not provide information about the fact that an EudraCT number also has to be requested in case of paediatric trials which are part of a PIP and which will be conducted in third countries only. For these trials sponsors will also have to complete a EudraCT application form (commission communication 2009/C28/01). These trials are not in the scope of this guidance because no authorization has to be requested to EU Competent Authorities but it would be good to mention them so that sponsors are aware of this requirement.	

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Section 2.4 Paragraph 4 p. 11/37		**Comments:** It is stated that a copy of the XML file on disc should be submitted. As some CA allow the electronic submission by other means (e.g. email) the text should be amended to allow for submission pathway as well**.** **Proposed change:** The applicant should save the full application form data set as an XML file using the utilities feature linked to the form on its webpage and submit a copy of this XML file on a disc **or electronically** with the application.	
Section 2.5 p. 11-13/37		**Comments:** It would be better to simply reference the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) rather than attempt to summarise it in a few paragraphs. **Proposed change:** "With regard to first-in-human clinical trials, the safety of participants can be enhanced by identification and planned mitigation of factors associated with risk. Detailed guidance for first-in-human clinical trials is available at: http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf"	
Section 2.6 4th paragraph p. 13/37		**Comments:** In the guideline "CHMP/QWP/185401/2004 final" in section 3. Information on the chemical and pharmaceutical quality of authorised, non-modified test and comparator products in Clinical trials, it is mentioned: *For test and comparator products to be used in clinical trials which have already been authorised in the EU/EEA, in one of the ICH-regions or one of the Mutual Recognition Agreement (MRA)-partner countries, it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA.* *From ICH countries or MRA partners, local product information equivalent to*	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		the SmPC should be accepted. **Proposed change:** The approved Summary of Product Characteristics ("SmPC") may replace the IB if the IMP is authorised in any Member State, ICH Country or MRA partner and is used according to the terms of the marketing authorisation**.Where an SmPC is not available (i.e. for products approved in the ICH countries or MRA partners), the equivalent locally-approved labelling (translated as necessary) should be accepted.** *"* **Please add the following definitions:** *** EU: European Union – 27 member states / EEA: European Economic Area = EU plus Norway, Iceland and Lichtenstein** *** ICH regions : EU/EEA – US - Japan** *** MRA countries: having GMP mutual recognition agreement with EU meaning that equivalent standards of GMP are assured: Canada – Japan – Switzerland – Australia – New Zealand**	
Section 2.7 Paragraph 5 p. 14/37		**Comments:** It would be helpful in particular for international trials if there was more flexibility on the structure of the dossier. **Proposed change:** "products in clinical trials. **Suggested** headings are reproduced in attachments 1-3. **Alternative headings e.g. those applicable to eCTD format, may also be used."**	
Section 2.7.1 1st sentence p. 15/37		**Comments:** For marketed non-modified comparator biotechnology products from an EEA country, the competent authorities should not require any additional viral information. **Proposed change:**	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		"Viral data should be provided for biotechnology IMPs, with the exception of marketed products from an EEA country when used according to the instructions provided in the SmPC."	
Section 2.7.1 9th sentence p. 15/37		**Comments:** **'**In exceptional cases, where impurities are not justified…' Is this statement to reference a specific batch release authorisation? If so please clarify and provide further details on the requirements and process, otherwise provide examples which describe the intention of this statement or if not appropriate consider deleting statement. **'**Where applicable, the TSE Certificate and viral safety data should be provided'. We disagree since appropriate TSE and viral safety information are provided within the quality section of the IMP, and it should not be necessary to supply certificates (signed or unsigned) **Proposed change:** "Appropriate TSE and viral safety information should be provided within the IMPD. Copies of TSE certificates or additional TSE statements are not required."	
Section 2.7.3 3rd sentence page 17 p. 17/37		**Comments:** EFPIA member companies committed to the transparency of clinical trials sponsored by them, regardless of whether these are performed within the European Union or outside. As such, EFPIA member companies committed to display descriptive clinical trial information and results of all confirmatory clinical trials and all exploratory efficacy trials. Thus information on clinical trials from 3rd countries will also be displayed. However, this is a voluntary initiative and thus a justification for the lack of display should not be requested for a clinical trial authorization in the EU. **Proposed change:**	

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		Delete the bullet.	
Section 2.8 4th sentence p. 18/37		**Comments:** To be in line with "CHMP/QWP/185401/2004 final" guideline, also products approved in MRA countries should be accepted. **Proposed change:** 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 SmPC **(or respective local labelling)** and has been assessed previously as part of a marketing authorisation in any Member State, in an ICH country **or in MRA partner countries.**	
Section 2.8.5 p. 20/37 1st / 2nd / 3rd row		**Comments**: The table suggest that an IMP in any ICH country can be used in the clinical trial in EU. This should be consistently added to the table (row 2 and 3) and extended to MRA countries. It should be clarified that the respective local labelling in the ICH / MRA countries is acceptable instead of the SmPC.	
Section 2.9 p. 20-21/37		**Comments:** • We strongly encourage a revision of the Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in clinical trials to achieve a greater European harmonisation within the existing legal framework. 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. • 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.	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change: 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 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.**	
Section 2.10 p. 21/37		**Comments:** The Paediatric Investigation Plan ("PIP") summary report, the opinion of the Paediatric Committee and the decision of the EMEA should only be included if the CTA concerned covers a trial in the paediatric population. **Proposed change:** **"If the trial is part of a Pediatric Investigational Plan ("PIP"),** the summary report, the opinion of the Pediatric Committee and the decision of the EMEA."	
Section 2.10 Bullet 2 p. 21/37		**Comments:** A list of national competent authorities to which the sponsor has already made the same application with details of their decisions is requested as attachment to the cover letter. As all information is available to Member States through EUDRACT, and the information is changing on an ongoing basis, it is preferred that competent authorities refer to EUDRACT to obtain this information. **Proposed change:** Delete this request.	
Section 3.1 p. 21/37		**Comments:** Sponsors frequently receive requests from National Competent Authorities to be immediately notified/informed of non-substantial changes. The text could be strengthened to discourage such requests. **Proposed change:**	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		"Notification/submission for information is only obligatory if the amendment is substantial or otherwise significant. Directive 2001/20/EC does not require notification nor immediate submission for information of non-substantial amendments. *As a general rule, such changes should instead be recorded and if appropriate included in a next update and be available on request for inspection at the trial site and/or the sponsor's premises as appropriate. "*	
Section 3.1 p. 21/37		**Comments:** According to Article 10(a), it is the role of the sponsor to make the decision on whether an amendment to a clinical trial meets the criteria of a substantial amendment requiring notification or not. The guideline could usefully clarify this point. **Proposed addition :** "The sponsor is required to make a decision on whether an amendment to a clinical trial is substantial.	
Section 3.1 p. 21/37		**Comments:** A definition of 'otherwise significant' is not given. According to note 41 this is not necessary because substantial has a wide notion and 'otherwise significant' therefore is of minor relevance. It is unclear to us why this confusing addition was made and we propose to delete any reference to 'otherwise significant'. **Proposed change:** Amendments to the clinical trial are regarded as substantial ~~and "otherwise significant"~~ where they are likely to have a significant impact on: Delete note 41.	
Section 3.2 Paragraphs 4 & 5 p. 22/37		**Comments**: We would propose that the last sentence of both paragraphs be changed to clarify that the meaning of "them" in the context of both paragraphs. **Proposed change**: In the 4th paragraph it is understood that "them" apply to amendments that the data in the ASR may require. We would propose replacing "them" with "such amendment(s)".	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		See the next comment for the 5th paragraph regarding IB updates	
Section 3.2 Paragraph 5 p. 22/37		**Comments:** The guidance states that the rules for notification of substantial amendments may apply to changes included in the annual update of the IB. If, however, an annual IB update concerns a change that has previously been notified as a substantial amendment in its own right (e.g. the IB has been updated to reflect new information already added to the IMPD), there should be no need to submit another substantial amendment notification. **Proposed change:** "The annual update of the IB in accordance with Article 8 of Directive 2005/28/EC is not *per se* a substantial amendment. However, the sponsor has to verify whether the update relates to changes which are to be considered as substantial. In that case, the rules for notification of substantial amendments apply to ~~them~~ that update, unless the update relates to a change (e.g. new data) that has previously been notified as a substantial amendment."	
Section 3.2 Paragraph 6 p. 22/37		**Comments:** The revised guideline clarifies that changes of sponsor contact details (e.g. change of postal or e-mail address) are not considered to be an amendment provided the sponsor remains the same. The information should nevertheless be transmitted to the National Competent Authority. In practice, a change of contact entails a change to the EudraCT .xml file. The issue is that some National Competent Authorities currently regard *any* change to the xml file as a *substantial amendment* by default. If changes in the contact details of the sponsor are not considered as an amendment, then they should not be sent to the CA neither to EC. In addition, some CAs do not wish to receive such information.	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		Proposed change: *"Changes of the contact details of the sponsor (or applicant, local representative, sub-contractors) (e.g. a change of email or postal address) are not considered as amendment, if it remains identical. The fact that such a change may necessitate a change to the EudraCT. xml form is not by itself a reason to submit an amendment. ~~However, theis information should be transmitted to the national competent authority of the Member State concerned as soon as possible.~~"*	
Section 3.3 p. 22-23/37		**Comments:** EFPIA welcomes the removal of the previous Attachment 5, which did little to clarify whether an amendment is substantial or not, and the inclusion of examples of changes that would typically be considered as non-substantial amendments. In view of the experience with the clinical trials directive rather more examples of changes that would **categorically** be regarded as non-substantial would have been expected and useful. This is for instance the case of "Extension of shelf-life and/or extension of the storage conditions on the basis of additional data with unchanged shelf-life specifications (provided certain conditions are met)"*CHMP/EMEA *'Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials'*	
Section 3.3.1 p. 23/37		**Comments:** The examples of protocol substantial amendments, although useful are not written in language that is consistent with that used in the criteria for substantial amendments. Specifically, the examples repeatedly use the term "this might/could significantly affect/impact…" rather than "likely to have a significant impact on…" **Proposed change:** "With regard to the protocol, the following is a non-exhaustive list of	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		amendments which are typically "substantial": • Reducing the number of clinic visits that significantly impacts on the safety or physical or mental integrity of the subjects; • Introducing a new monitoring procedure that significantly affects the conduct or management of the trial; • The use of a new measurement for the primary endpoint that significantly alters the scientific value of the trial; • Changing the definition of end of trial that significantly impacts the scientific value of the trial; • Changing a principal or co-ordinating investigator that significantly impacts the conduct or management of the trial; • Addition of clinical trial sites…"	
Section 3.4 p. 25/37		**Comments:** A few examples are given where the assessment responsibility between the Competent Authority and Ethics Committee, respectively, is relatively clear. Unfortunately, the primary responsibility is in many other instances unfortunately much less clear for all stakeholders. In fact, we have the impression that 'overlapping' assessments may be a growing issue and sometimes resulting in conflicting outcomes (EC vs. CA). **Proposed change:** General examples can be provided where the assessment responsibility can be clearly assigned (e.g. changes impacting scientific impact should normally be notified to the Competent Authority). Member states should be encouraged to clarify their legal requirements to meet the requirements of the proposed directive. When an amendment is filed to one body e.g. CA or EC, the other **only** needs to receive the substantial amendment form and not for a copy of the whole file.	

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		This section should be changed to reflect, "To provide this information it is sufficient to submit only the SA form once the decision… It should be made clear that the substantial amendment Annex 2 form should not be used to provide non-substantial amendments 'for information only'.	
Section 3.5 Paragraph 3 (c) p. 26/37		**Comments:** A track-change version is a new requirement. Alternative methods which clearly describe the proposed amendment and identify the changes from the previous submission should be allowed as long as there is a clear description of the change and the data presented to support this change. If the track change applies to the IB, it would have a great impact on work practices and would be very time consuming for both the applicant and the assessor (very long document). A statement that the rest of the IB is unchanged should be sufficient**.** The need for tracked changes should be restricted to protocols. In addition, "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 reviewers friendly to highlight the relevant changes in a summary table. **Proposed change:** Delete "in track-change version". ***"****In this case, an additional table should* ***summarise [instead of list]*** *the amendments to the documents."*	
Section 3.5 Paragraph 3 (f)		**Comments:** This section states that a print out copy of the revised application form should be provided, showing the amended fields highlighted. *I*n case of electronic only	

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p. 26/37		submissions, the addition of highlights on the xml form is not possible. Applicant should indicate in the amendment form which section numbers of the XML file have been altered as part of the amendment Only in some countries, the XML file is attached in a paper document (e.g. in Spain, there is a telematic system in place). In addition the word "form" could be changed to 'form or page(s)"; in case only one item on one page is changed this will save a lot of paper for the applicant, since the application form can be made of 50+ pages. **Proposed change:** To delete "a print out of the" and leaving: "by attaching a revised form/page(s)…"	
Section 3.6 p. 27/37		**Comments**: Directive 2001/20/EC (Article 9.4 and 9.6) only defines the possibility for additional assessment time for "clinical trials involving medicinal products for gene therapy, somatic cell therapy including xenogenic cell therapy and all medicinal products containing genetically modified organisms." As such it may be appropriate to also limit the possibility for the extension of assessment time for amendments to these products' submissions (as was the case in the previous revision of the guideline) and not extend it to other products.	
Section 3.6 p. 27/37		**Comments:** It is indicated that the CA should respond 'within 35 days from the receipt of a **valid** notification' This is unlike the original CTA were the validation is included in the 60 days review time. This should be similar for amendments. **Proposed change:** 'the national competent authority should respond within 35 days from receipt of the ~~valid~~ notification of an amendment. ***The validation of the notification thus forms part of the delay of 35 days.***	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
Section 3.6 Paragraph 2 p. 27/37		**Comments:** The current version of the guideline (Version 2) states that *"(…) as guidance, the amendment may be implemented after 35 days from the receipt of a valid notification of an amendment if the CA has not raised grounds for no acceptance."* The new version instead stresses that *"(…) as guidance, and in view of the approval time for requests for authorisation, the national competent authority should respond within 35 days from the receipt of the valid notification of an amendment."* While probably unintended, the revised text may give the impression that a tacit approval (if no grounds of non-acceptance have been received during the 35-period) is no longer possible. The possibility of a tacit approval thus needs to be re-instated. **Proposed change:** *"(…) If the national competent authority states, prior to expiry of the 35 days deadline, that it raises no grounds for non-acceptance, the sponsor does not have to await the expiry of the 35 days deadline. As guidance, the amendment may in any event be implemented after 35 days from the receipt of a valid notification of an amendment if the CA has not raised grounds for nonacceptance."*	
Section 3.7 Paragraph 2 Bullet 2 p. 27/37		**Comments: Examples for urgent safety measures are as follows:** • a trial is halted following the recommendations of a Data Safety Monitoring Board on the grounds of patient safety or a lack of efficacy; Lack of efficacy is not always grounds for an urgent safety measure. This needs to be qualified to state where lack of efficacy is likely to have an effect on the safety and/or wellbeing of the subject(s) **Proposed change:**	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		a trial is halted following the recommendations of a Data Safety Monitoring Board on the grounds of patient safety or a lack of efficacy where this is likely to have an effect on the safety and/or wellbeing of the subject(s)	
Section 3.10 Paragraph 3 p. 30/37		**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 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"*	
Section 4.1 p. 30/37		**Comments:** Considerable uncertainty and confusion persist regarding the proper end of trial definition. In particular this is true for trials where the active treatment phase is followed by a long-term follow-up or observation period. Moreover, the first type of end of trial declaration (when the study is terminated within a given Member State but not worldwide) often triggers a (mistaken) expectation for a medical summary report. **Proposed change (the following two paragraphs are consecutive in the text):** **Paragraph 4.1:** *"End of the trial" is not defined in Directive 2001/20/EC. The definition of the end of the trial should be provided in the protocol and any change to this definition for whatever reason should be notified as a substantial amendment. In most cases it will be the date of the last visit of the last patient undergoing*	

Section No + Paragraph No + Page No	Stakeholder No.	Comment and Rationale; proposed changes	Outcome
		the trial enabling an evaluation of the primary outcome measure. Any exceptions to this should be justified in the protocol." **Paragraph 4.1:** *"For multinational trials, the sponsor should make an end of trial declaration (…) twice, i.e., when:* • *The trial ends in the territory of the member state concerned. The sponsor should specify that the trial is still ongoing at investigational sites in other countries. In case the end of trial (as defined in the protocol) is to be followed by a patient observation/follow up phase, the Sponsor should duly inform the concerned Member State(s) in a cover letter.* • *The complete trial has ended (as defined in the protocol) in all participating centers in all countries within and outside the Community. This end of trial declaration triggers the generation of a clinical trial summary report (see paragraph 4.3)."*	
Section 4.2.2 & attachment 3 p. 31/37		**Comments:** On the Annex 3 notification form in section D.3.1 it should be clarified whether one should specify here the date when the trial is halted (i.e. the decision is made or when the administration of treatment is interrupted) or the anticipated date of Last Patient Last Visit (which may be several weeks later due to further follow-up visits	
Section 4.3 p. 31/37		**Comments:** Contrary to what is stated in the draft guideline, the clinical trials summary report is not part of the end of trials notification. Directive 2001/20/EC requires only that the competent authority and ethics committee are notified "that the trial has ended" (Article 10(c)). The only explicit requirement for submission of a trial report in EU legislation relates to paediatric clinical trials involving medicinal products authorised in the Community (Regulation 1901/2006,	

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		Article 46), which are to be submitted within 6 months of completion of the study. In addition, the current version of this guideline indicates that a summary of the clinical trial report should be provided within one year of the end of the trial. These timelines should remain the default. **Proposed change:** "~~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.~~ The sponsor should provide a summary of the clinical trial report following the end of the trial to the competent authority of the Member State(s) concerned. The summary should be provided within 6 months of the end of the trial for paediatric clinical trials involving medicinal products authorised in the Community (Regulation 1901/2006, Article 46), or within 12 months of the end of the trial for all other clinical trials conducted in the Community."	
Attachments 1, 2 & 3 p. 32-37/37		**Comments:** Headings proposed. **Proposed change:** Strictly speaking these headings are not CTD as they are all prefixed 2.1 (Quality), 2,2 (Non-Clinical) and 2.3 (Clinical). If they were truly CTD headings they would be prefixed with a 3.2 (Quality), 4.2 (Non-Clinical) and 5.x (Clinical) in line with CTD Modules as follows: 2.1.S.1 General Information becomes 3.2.S.1 General Information 2.1.S.1.1 Nomenclature becomes 3.2.S.1.1 Nomenclature It would be beneficial for the CTD headings (and numbering) to be fully adopted in the IMPD. If the guidance cannot be changed, can we suggest that it is stated in the	

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		guidance that submission of an IMPD numbered consistently with CTD would still be valid	