MINISTERIO DE SANIDAD Y POLITICA SOCIAL

agencia española de medicamentos y productos sanitarios

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ASUNTO **Comentarios de la AEMPS a la Guía de la Comisión sobre ensayos clínicos en consulta pública**

DESTINATARIO **Subdirección General de Relaciones Internacionales Ministerio de Sanidad y Política Social**

agencia española de medicamentos y productos sanitarios
13 OCT 2009
DE LA UE
SALIDA Nº 213

Se adjuntan comentarios de la AEMPS relativos a la "*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*" en consulta pública por la Comisión Europea, solicitando su remisión a las Autoridades Comunitarias competentes.

LA DIRECTORA

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DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS SANITARIOS

Draft revision 3 [...] 2009 "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 the
AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS
(AEMPS)

30th September 2009

The AEMPS welcomes the Commission's initiative in reviewing 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", and giving the stakeholders the opportunity to send comments on it. This is an important document which enters into details to improve harmonisation in the requirements referring to notifications by sponsors to the Competent Authorities, and also has some influence on the standard of documents required in the CT applications submitted to Ethics Committees. Please find herewith the following observations from the AEMPS:

1. Main comments and proposals

Section 2. Request for a clinical trial authorisation

- The second paragraph on section 2.1.2. should be amended or deleted

  Art. 9.4 of Directive 2001/20/EC states: "Consideration of a valid request for authorisation by the competent authority ... may not exceed 60 days". Also in art. 6 5 it is stated "The Ethics Committee shall have a maximum of 60 days from the date of receipt of a valid application to give its reasoned opinion..." We understand that the concept of valid request implies that the Competent Authority or the Ethics Committee acknowledges receipt of a valid application. Therefore, validation of the request for authorisation thus does not form part of the delay of 60 days.

  This interpretation is consistent with the Commission's one stated in Question 9 of the Q & A document in vol 10 of Eudralex: "Question 11: Will the 60 day approval period commence when a valid application is submitted or when the Ethics Committee notifies the Sponsor that the application is valid? Answer: The 60 day approval period commences when Ethics Committee has informed the sponsor that it has reached the conclusion that the application is valid.

- In section 2.4., first paragraph

  - The reference for the application form should be the application form document published on Eudralex vol 10 and not the "Detailed guidance on the European

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clinical trials database" which needs to be updated in order to consider the last and future changes introduced in EudraCT.

- In section 2.4. information on (a) to (g) should be modified in order to be consistent with what is stated previous to the signature in the application form published in vol 10 Eudralex.

  The wording of f) in the guidance should be modified as follows:

  (f) The result-related information of the clinical trial to be made public will be submitted in accordance with the Commission Communications 2009/C28/01 and 2008/C168/02 for paediatric clinical trials and non-paediatric clinical trials respectively after the end of the clinical trial[22]

- In Section 2.6,

  - at the end of the last paragraph, it is proposed to add the following sentence: "Therefore, this document should clearly define what kind of adverse reactions are not subject to expeditive reporting."

    This is important, since the IB is the reference document for the assessment of expectedness.

- In Section 2.9, in order to assure homogeneity of requirements, the last paragraph should be amended in order to mention adherence to the standard developed by the CTFG. This standard could be integrated as an appendix of this guideline.

Section 3 Notification of amendments

1. Traceability of amendments in the file of a clinical trial is important and it is a Good Clinical Practice requirement. Considering that an amendment could include several changes, the amendment code number is essential for its identification. However, in practice we see often the following mistakes in the applications received in the AEMPS: the amendment has not an amendment code number, or the same amendment is identified with a different amendment code number in the AEMPS and in the Ethics Committee applications, or the same amendment is identified with different code numbers in the applications submitted to different Competent Authorities. Therefore, the importance of an unique identification of the amendment should highlighted in the guideline. In our opinion it would be of interest proposing examples of how different type of amendments could be identified on an international trial giving a message that the amendment code should remain invariable.

   For example, if the amendment involves all participating countries the code number could be INT1 to INTn.

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If the amendment is specific for a country (e.g. addition of new sites) the code number could start with the letters representing the country SP1 to SPn, etc.

- In section 3.3.2:

  - It is proposed that chapter 8 of the "Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials" would be the only document containing the classification for amendments related to the quality part of the IMPD.

  - "Minor changes in the labelling of the investigational medicinal product" should be deleted.

    Labelling is not referenced in this guideline as a document to be provided in a CT application. However, it is mentioned that minor changes to the labelling of the IMP are non substantial amendments, as if major changes were substantial amendments. The concept of minor is not clear.

- In section 3.5:

  - At the end of second paragraph, it should be added the following: "In these cases, the documentation should include the amendment form accompanied if applicable of the updated XML of the application form for each of the concerned clinical trials together with one single copy of the supportive documents."

    In (a), third bullet point should include some more explanation about the amendment code. It is proposed to add "The amendment code number should be unique for every substantial amendment within a clinical trial and will be the common identifier of the amendment for the Ethics Committees and Competent Authorities in all concerned countries.

- In section 3.11, it is proposed to change the wording as follows: "The sponsor ~~does not have~~ should not notify the national competent authority or the Ethics Committee of non-substantial amendments...."

  This in order to put more emphasis in the fact that non substantial amendments should not be received by CA or EC.

Section 4 Declaration of the end of a clinical trial

- In section 4.3, the wording in the previous version of the guideline was clearer.

  Notification of the summary of results to be made public is independent of the obligation of the sponsor to provide to the Competent Authority and the Ethics Committee with a summary of the clinical trial report within one year of the end of the trial.

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This requirement was in the previous version of the guidance and is mandatory in the national legislation.

- With respect to section 4.4:

  - It would be very useful to include in this section a clarification with respect to what should be the information that would be necessary to report after a clinical trial has been finished in a MS but not overall. In this respect, SUSAR reporting and annual safety reports should only be provided when they would contain information which is relevant for the safety of the subjects who have participated on the CT.

2. Other comments

- In Section 2.2.:

  - Other remarks proposed to be added in the covering letter are: (d) alert that the submission of the quality part of the IMPD will be done by someone different from the sponsor, (e) highlight changes made to the previous application in case of a resubmission.

  - The last two paragraphs should be deleted.

    The first one, because the PIP required information will be already included on the first/second page of the CTA form. The second one, because in the last paragraph of section 2.6 of this guideline it is already clarified that the reference document for the assessment of the expectedness of any adverse reaction will be the IB or equivalent document.

  - It is proposed to replace "The applicant should indicate where the relevant information is contained in the application dossier" with "An index of the documents provided on the CT application should be provided."

- In Section 2.1.4.3., the first paragraph, "The initial contact should be by telephone and for reasons of traceability..." should be modified to "The initial contact could be by telephone, and for reasons of traceability....".

  The telephone contact should not be mandatory. We would prefer an initial contact by e-mail or FAX.

- In section 2.3., the reference to the EudraCT database in the second line should be modified to "EudraCT Community Clinical Trials System" giving if possible the URL for EudraCT. The referred guidance needs to be updated.

- In section 2.4., first paragraph:

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- The URL for EudraCT should be given as a reference where the application form could be filled in and as a place where other helpful information could be found.

- In section 2.4, the sentence "More information about EudraCT application form is available here:" should be modified to "More information about EudraCT and how to fill in the application form is available here:"

  The application form in volume 10 is identified as Annex 1: clinical trial application form (not as EudraCT application form).

- In section 2.5.:

  - The second paragraph should be modified as follows: "... It should be identified by the title, an invariable sponsor's protocol code number specific for all versions of it, a date and a number of version that will be updated when it is amended....."

    It is important to emphasize that the sponsor's protocol code number (this is the term in the application form) should remain invariable along the CT. Date of the protocol should always be mandatory and it is preferable to the version in case only one of them is given. Therefore, it is proposed to put it in the first place in order to emphasize this.

  - With respect to the content the protocol should include the publication policy as per art. 4 of the Commission Directive 2005/28/EC.

  - Number of Directive 2005/28/EC in the third paragraph should be amended. It says 20005/28/EC.

- In section 2.7.1.

  - It would be of interest that when the IMP does not have a marketing authorisation and it is manufactured outside the EU, a copy of the manufacturer's authorisation by the corresponding competent authority in the country where it is placed is provided.

  - Paragraph 7th should be modified as follows "- certification of the GMP compliance ..."

- In Section 2.8.3, the title should be amended: Possibility to refer ~~to the Posibility to refer~~ to the SmPC.

- In Section 3.2,

  - First paragraph should be modified as follows: "Substantial amendments as referred to in article 10(a) of Directive 2001/20/EC are only those which are introduced after ~~approval~~ authorisation of the clinical trial by the national

competent authority ~~or~~ and the favourable opinion by the Ethics Committee ~~respectively~~."

Art. 10(a) of Directive refers to amendments after the commencement of the CT. This requires both the CA authorisation and the favourable opinion by the EC.

- In the second bullet point, the second line, "....authorisation by the Ethics Committee...." should be changed to "....opinion by the Ethics Committee...."

- In Section 3.3.1.:

  - In the second bullet point, "or a change in the principal investigator" should be deleted, since the fifth bullet point refers to this circumstance.
  - "minor changes in the recruitment procedure" as a not substantial amendment should be modified to "Prolongation of the recruitment period without change to the duration of the clinical trial"

  Assessment of the recruitment procedure is normally a competence specific of the Ethics Committees.

- In section 3.3.2:

  - Last paragraph of section 3.3.3 corresponds to section 3.3.2.

- In section 3.4, the following paragraph should be added at the end: "Changes that only require the assessment by the Competent Authority should not be mixed with changes requiring that require the assessment by the Ethics Committee in the same Substantial amendment, and vice versa, changes only requiring the assessment by an Ethics Committee should not be mixed with changes requiring the assessment of the Competent Authority".

- In section 3.5:

  - At the end of second paragraph, it should be added the following: "In these cases, the documentation should include the amendment form accompanied if applicable of the updated XML of the application form for each of the concerned clinical trials together with one single copy of the supportive documents."
  - In (a), first bullet point, "sponsor protocol number should be changed to "sponsor protocol code number".
  - In (c), second bullet point, fourth line "....number of version and date." Should be modified to date and number of version in order to emphasize the importance of the date.
  - In (f), the EudraCT application form should be replaced by the "clinical trial application form".

- In foot note 44, "...version and date..." should be changed to "date and version" in order to emphasize the date in first place. At the end it should be added that in a translated document the date should be the same as in the original document.

- In section 3.7:

    - In eight paragraph starting "Urgent safety ..." last sentence should be modified to "This could be done by telephone and preferably for reasons of traceability~~, also~~ by e-mail or fax in the first place followed by a written report as a substantial amendment".

      We prefer the notification by e-mail or FAX rather than by telephone. It is important to emphasize that the written report is as a substantial amendment.

      Adding substantial amendments at the end of 8th paragraph, permits to delete first bullet point bellow that paragraph "notify substantial amendments (cf. above).

- With respect to section 4.4:

    - Title would be clearer if modified to "Follow-up after the end of the clinical trial.

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