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ASUNTO **Comentarios de la AEMPS al Concept Paper de la Comisión sobre ensayos clínicos**

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Se adjuntan comentarios de la Agencia Española de Medicamentos y Productos Sanitarios sobre el *Cocept paper* de la Comisión Europea relativo a la revisión de la Directiva 2001/20/CE sobre ensayos clínicos, solicitando su traslado a las autoridades comunitarias correspondientes.

LA DIRECTORA

agencia española de medicamentos y productos sanitarios
DIRECCIÓN

Belén Crespo Sánchez-Eznarriaga

CORREO ELECTRÓNICO
sdaem@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 51 30
FAX: 91 822 50 10

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DE MEDICAMENTOS Y
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SANITARIOS

Comments of the *Spanish Agency for Medicines and Medical Devices* (AEMPS) on the European Commission's concept paper regarding the revision of the «Clinical Trials Directive» 2001/20/EC

8th June 2011

The ***Spanish Agency for Medicines and Medical Devices***, welcome the Commission's initiative to propose practical options addressing some of the key issues of the directive 2001/20/EC (CTD), and thanks the opportunity to send comments to these proposals.

1. Cooperation in assessing and following up clinical trial applications (CTA)

Consultation item no. 1: Do you agree with this appraisal? Please comment.

The AEMPS endorses the principle of a single EU portal. All necessary notifications to the MS concerned (MSC) should be done through this Portal, and not only initial applications and substantial amendments.

Applications through the Portal should be mandatory for all CT. However, a step-wise implementation should be proposed, starting with multinational CT for which a coordinated assessment is performed.

The proposed EU portal should either distribute or make accessible applications to the concerned MS, in a way that would make easy the subsequent distribution of the corresponding information to the national competent authority (NCAs) and/or Ethics Committee (EC).

The submission process through this EU Portal should take into consideration that certain documents should be MS specific and in local language (normally to be assessed by EC in most MS).

This EU single portal for CT applications could be managed either by EMA or the network of European medicines agencies (Heads of Medicines Agencies, HMA). The Commission is invited to evaluate the most efficient and the low cost solution for the development and the location (at EMA level or at HMA /one NCA level). However, the EU single portal for CT applications should be under the functional coordination of the Clinical Trials Facilitation Group (CTFG) proposed as coordination body for this

CORREO ELECTRÓNICO
sdaem@aemps.es

C/ CAMPEZO, 1 – EDIFICIO 8
28022 MADRID
TEL: 91 822 50 28
FAX: 91 822 50 10

procedure (see bellow). The Commission should clarify if the manager of the Portal will charge for the service and how this will impact on fees.

The Commission also proposes three options to give legal support to the Member States (MS) cooperation in "assessing and following up applications for CTs". However, these options only consider the assessment collaboration for initial CT applications and for substantial amendments. It is proposed that such cooperation would also apply to the assessment of safety issues (e.g. SUSAR, DSUR, and any safety concern that could appear along the CT conduction) that nowadays represent a great burden for national competent authorities, ethic committees and sponsors.

1.1. Single submission with separate assessment

Consultation item no. 2: Do you agree with this appraisal? Please comment.

The AEMPS agrees that this system is not the most appropriate for multinational CT. However, taking into account that 75% of the CT performed in EU are conducted in only one MS, the principles of national assessment and authorization should also be maintained.

1.2. Single submission with subsequent central assessment

Consultation item no. 3: Do you agree with this appraisal? Please comment.

AEMPS fully agrees with the Commission preliminary appraisal. The process as it is proposed is not the most appropriate for CT authorisation, it would be costly, inefficient, and would not be workable in practice.

1.3. Single submission with subsequent "coordinated assessment process" (CAP)

1.3.1 Scope of the CAP and 60 days timelines

The AEMPS strongly supports the principle of a coordinated assessment by the concerned MS and the coordinated assessment procedure is the preferred option. The principle of maintaining the CT authorisation at the national level, even in the case of multi-national clinical trials is also supported. This would allow the MS to ensure their own responsibilities on CT conducted in their territories.

Consideration should be given to expand this coordinated evaluation to the issues related to safety monitoring after the CT has started (e.g. SUSAR reporting, DSUR, and assessment of any other reported safety issue).

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In order to ensure feasibility of this procedure, a valid CT application should be received at the same time in all concerned MS at the corresponding competent authorities and/or Ethics Committees.

Clear rules for choosing the "reporting Member State" and also for expanding the participation in the CT to new Member States once the CAP decision is made should be addressed in the proposal.

The CTFG should be recognised as the body in charge of co-ordinating the CAP. An appropriate management of documents during the assessment process would be necessary. The CTFG should have a legal basis maintaining a functional dependence of HMA.

The secretariat of CAP should be ensured by the HMA CTFG and not EMA due to the fact that only the MS are involved in CT decision. The VHP experience by the CTFG can be taken into account to build up this secretariat whereas EMA is responsible for maintaining the CT databases (EudraCT and EVCTM).

The CAP would benefit from the Voluntary Harmonization Procedure (VHP) experience among NCAs which has shown that harmonisation in assessment needs:

- MS to have a common scope of assessment and objectives, the same general principles on CT assessment and the same process (same dossier, simultaneous application, same time lines),
- Appropriate IT tools to share documents and assessments, and a data management system, including tracking system,
- An administrative coordinator of the system,
- MS assessment to be supported by a leading Member state per CT,
- All MS to participate in the system at the same time.

Although a minor aspect, the acronym CAP for a "coordinated assessment procedure" of CT might generate some confusion with the "centralized authorized products" (also known by CAP especially in the context of quality control). Thus, we suggest changing the acronym CAP for other like "CT-CAP", "CT-CP" or other.

Consultation item no. 4: is the above catalogue complete?

Consultation item no. 5: Do you agree to include the aspects under a) and only these aspects in the scope of the CAP?

Aspects considered in a) are general enough to consider that all necessary aspects of a CT risk-benefit assessment are covered, including appropriateness of the CT

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population, measures to mitigate risks, etc. However, the following changes are proposed:

- "Traceability" should be replaced for "labelling" in the title of section a);

- Non investigational medicinal products could be used off-label or could be non authorised medicinal products, and need to be included in the CT assessment. Therefore, the first bullet point should refer to the characteristics and knowledge of the medicinal products intended for the clinical trial instead to the IMPs. On the other hand, the reference to "compliance with the requirements for labelling of... " should be modified to "compliance with the requirements for ensuring traceability of ...." taking into consideration that labelling is only mandatory for IMPs

- Under "the relevance of the trial", it should also be mentioned "including justification for the research on the intended population, especially when that includes minors or other vulnerable population."

- A more general reference to the completeness and adequateness of the clinical trial documents (protocol, IMPD, IB, etc.) would be preferable instead of limiting it to the investigator's brochure.

AEMPS agrees to include the aspects under a) and only the aspects under a) in the scope of the CAP. National assessment on b) and c) needs to run in parallel with the CAP procedure, and will sum up to the single MS final decision on the CT to be given by the competent authority.

In Member states requiring assessment of the protocol by both a competent authority and an Ethics Committee, there is some inevitable overlap in the protocol and Investigator's Brochure assessment. The proposal should include a mandate for the NCA to coordinate all these assessment bodies to be able to raise a single opinion by MS.

In addition, aspects such as the adequacy of the comparator groups, or the acceptability and feasibility of certain follow-up monitoring measures are aspects which require an assessment taking into consideration which is the local clinical practice. However, AEMPS recognises the importance for the sponsor of getting an EU agreement on the aspects included under a), in order to make possible having a single multinational protocol valid for all MS. So, the process will need to integrate the view from EC. A systematic exchange of information between NCA and EC would be necessary in order to have the overall MS opinion on the CT during the CAP. This could be difficult with respect to the initial CT assessment, but turns to be more complicated in case of substantial amendments.

The involvement of Ethics Committees in the CAP would be very challenging and probably require changes in the national organization of these Committees, in order to make possible a higher frequency of their meetings and also the necessary exchange of information between the EC and the CA. In this exchange of information the independence of the EC should be preserved.

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It is considered essential that timelines for the CAP are equivalent to those for EC. Therefore, a clock stop should be included in the CAP procedure; the timelines for the assessment of the initial application should be those in the current CT Directive, and therefore, 90 days in the cases of CT on genetically modified organisms and advance therapy IMP.

1.3.2 Disagreement with the assessment report

Consultation item no. 6: which of these approaches is preferable? Please give your reasons.

AEMPS do not endorse any of the proposed options :

- The first one because any serious risk to public health or to subject safety raised by one MS should also be considered as such by the others;
- The second option would mean that a MS would be obliged to accept a CT to be conducted in its own territory despite its major concern, which does not seem acceptable for a voluntary activity.
- The third one because any referral would lengthen the process and make the EU clinical trials much less attractive than at present. In addition, neither the Commission nor the Agency are responsible for the assessment of CTs.

On the basis of the VHP experience, it can be assumed that MS would try their best to achieve common decisions during the CAP procedure. However, MS which disagree with the majority should, in any case, be allowed to "opt-out", being transparent about their reasons. It should be clarified under which circumstances, if any, in the case of opting-out, the CT could be approved outside the CAP by a national procedure.

1.3.3 Mandatory/optional use

Consultation item 7: which of these approaches is preferable? Please, give your reasons

Considering that there is a huge variety of multinational CT, and also the fact that not all MS are currently assessing a CT application under the same timelines, it is proposed that the CAP should be optional for multinational CT at least during a transitional period.

After that transitional period, and on the basis of the gained experience, it could be analysed the usefulness of having a single EU procedure for all CT, where the single state CT will be assessed by the corresponding MS. Extending the CAP to single state CT would allow that the IMPD of any CT will always be available for all MS, and could allow cross references to that document in subsequent CT applications.

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1.3.4 Tacit approval and timelines

Consultation item 8: do you think such a pre-assessment is workable in practice? Please comment.

The AEMPS has the following comments:

- The principle of explicit authorisation is acceptable, meaning that if no decision is taken within the specified timelines the CTA application should be considered as not authorised.

- It is accepted that timelines for a CTA assessment should be those stated in the CT Directive (60 or 90 days that could be extended for a maximum of 90 days period) depending on the CT characteristics). However, a clock-stop (for a limited time period) should be included in the procedure. This would harmonize the timelines for the EC and CA and would give more flexibility to the procedure.

- It is proposed that timelines for substantial amendments (SA) should be those established in the CT Directive for the EC assessment (35 days). However, it should be possible to extend this period in the case of CT on advanced therapy or genetically modified organisms, depending of the type of SA. It should be clarified if the procedure would allow the submission to the sponsor of grounds of non acceptance before the final decision is taken. In case grounds for non-acceptance are allowed, there should be a clock stop in the procedure.

- Levels of risk should be standardized. Levels of risks defined in section «Risk assessment and monitoring» from the volume 10 Eudralex guideline "Ethical considerations for clinical trials on medicinal products conducted with the paediatric population. » could serve as a baseline reference.

- It is important to state that the notion of Type A (low risk) CT should not imply widening the scope of CT to include non-interventional studies. These studies should fall out of the definition of CT as explained in comments to consultation item 9.

- In relation to type A clinical trials definition:

  - A new condition is proposed for type A of CT: "*the IMPs are not modified for the purpose of being used in the clinical trial*", since in that case, the assessment of the adequacy of the manufacturing procedure and good manufacturing practice of facilities where the IMP is going to be modified would be needed. Also the term "insignificant risk" in part b) of definition needs to be clarified.

  - Condition a) mentions that all the medicinal products should be either authorized in a concerned MS or part of a standard treatment in a concerned MS. This can be interpreted as if in a multinational trial the medicinal products need only to be authorized in one of the participating MS. In this case, MS where the products

are not available should assess the suitability of the use of those medicinal products and the adequacy of the way of supply/traceability measures, considering the normal clinical practice. Insurance coverage could be considered necessary even in the case that it would not be mandatory for this type A CT.

- It is proposed that b) would not be a condition in the definition, although of course, the risk-benefit of the CT interventions would always be included in the assessment.

  Justification:

  Condition b) of the definition would require for a multinational trial that the CT interventions with respect to normal clinical practice are assessed in every MS, and introduces the possibility of discrepancies in the classification by MS. However, the implications in case a MS considers that the CT poses more than a minimal risk to the CT subjects could be limited: either the CT could be acceptable, but with certain national adjustments in the CT conduction (e.g. intervention measures could require more explanation in the subject information leaflet, an insurance could be necessary even in the case that it would not be mandatory for these type A CT, the place for doing the follow-up diagnostic measures could be outside of the participating sites, etc.) or the CT could not be acceptable for several reasons, including the lack of interest for that MS in participating in the CT. However, interventions implying a risk higher than minimum could be reasonable in certain cases, but would not be an obstacle for most of the simplification admitted for type A CT.

- The idea of pre-assessing the classification as type-A CT is acceptable. The criteria for defining low risk should be defined. These criteria should be as much objective as possible, in order to enable the sponsor to propose a preliminary classification for the CT. The acceptability of the classification should be considered within the assessment procedure. The deadline for that procedure should not excess 60 days. The type of simplified requirements for type A CT should be defined: e.g. simplified CT dossier (including a simplified CTA form), simplified safety monitoring on the basis of what is justified in the CT protocol, simplified or exempted DSUR, adapted monitoring and GCP compliance if appropriately justified by the sponsor, exemption from labelling where other measures in order to ensure traceability are justified. These CT also could benefit of a change in art.19 of Directive (see comments to Consultation topic nº 12).

2. Better adaptation to practical requirements and a more harmonised, risk-adapted approach to the procedural aspects of clinical trials

2.1. Limiting the scope of the Clinical Trials Directive

2.1.1 Enlarging the definition of "non interventional" trials

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Consultation item no. 9: Do you agree with this appraisal? Please comment.

The AEMPS considers that the new legislation on CT is a good opportunity for changing the definition of observational (non interventional) studies. The definition should be scientifically sound, being the main criteria the dissociation between the assignment of treatment and the decision for including the patient in the study, so that the assignment of the medical intervention which is object of assessment is not at the discretion of the investigator. This is in line with current definitions as the one from WHO and the International Committee of medical journal editors (ICMJE)[1]

The AEMPS proposes to modify the term "non interventional trial" to "non interventional study". In line with the statement above, the following changes are proposed with respect to non-interventional studies:

- Condition "a study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation." should be replaced by "a study where the medicinal product(s) is (are) prescribed in accordance with the terms of the marketing authorization or according to current clinical practice.
- "No additional diagnostic or monitoring procedures shall be applied to the patients" should be deleted from the definition.
- Compliance with good epidemiological practice should be requested

2.1.2 Excluding clinical trials by "academic/non-commercial sponsors" from the scope of the Clinical Trials Directive

Consultation item no. 10: Do you agree with this appraisal? Please comment.

AEMPS agrees with the Commission and considers that academic/non commercial studies should be maintained within the scope of the CT Directive. The view that it would be better to come up with harmonised and proportionate requirements for all clinical trials is also supported.

2.2. More precise and risk-adapted rules for the content of the application dossier and for safety reporting

Consultation item no.11: Do you agree with the appraisal; This approach would help to simplify, clarify, and streamline the rules for conducting clinical trials in the EU by providing one single, EU-wide, risk-adapted set of rules? Please comment.

[1] http://www.icmje.org/faq_clinical.html

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Consultation item no. 12: Are there other key aspects on which more detailed rules are needed?

AEMPS supports the proportionality of requirements based on the risk of the CTs. AEMPS also supports that risk to CT subjects and risk to data reliability are the elements defining the risk. However, we consider that simplification of the requirements should also consider the following:

- labelling for IMPs marketed in the MS where the clinical trial takes place could be exempted. In these cases, traceability of medicinal products to be used in the clinical trial could be ensured with alternative measures, such as recording of the prescription details (including name of the product, batch number and amounts dispensed) in the case report forms or having records of the dispatch by the pharmaceutical Service to the investigator.

- GCP and monitoring,

- insurance,

- DSUR should be exempted or simplified for CT on IMPs authorised in the EU, at least for type A CTs.

- The provision of the IMP free of charge for the sponsor should not be a general rule, given that it may constitute a problem for trials with marketed medicines. The general rule should be to ensure no expenses for the CT subject. Therefore, it is proposed that Art. 19 of Directive should be amended. Instead of "Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available **free of charge by the sponsor**" it would be better to stay that "Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration shall be made available free of charge for the clinical trial participants."

- In cases where investigational medicinal products are prepared in hospital pharmacy services, GMP standards could be substituted by accepted standards for the preparation of magisterial formula or officinal preparations.

- A reference to the criteria for making public information on all authorised CT in the EU clinical trials register would be welcomed.

2.3. Clarifying the definition of "investigational medicinal product" and establishing rules for "auxiliary medicinal products"

Consultation item no. 13: Do you agree with this appraisal that the combined approach (new definition for the 'investigational medicinal product' and establishing rules for 'auxiliary medicinal products') would help to simplify,

clarify, and streamline the rules for medicinal products used in the context of a clinical trial? Please comment.

Clarification of the IMP definition is welcomed. However, the placebo should be maintained as an IMP in the new definition proposed by the Commission.

The definition of auxiliary medicinal products could be "A medicinal product as referred to in Article 3(3) of Directive 2001/83/EC, with a marketing authorisation within the EU which is not an investigational medicinal product and is used in a clinical trial according to the protocol".

It should be clarified that any auxiliary medicinal product not authorised in any EU country should comply with the same requirements applicable to an IMP, and also that non-CE marked medical devices which are to be used in a CT on medicinal products should comply with the requirements for investigational medical devices established in the legislation for investigations on medical devices.

2.4. Insurance/indemnisation

Consultation item no. 14: Which policy option is favourable in view of legal and practical obstacles? What other options could be considered?

The AEMPS agrees with the Commission preliminary appraisal. Both policy options could be a viable solution.

2.5. Single sponsor

Consultation item no. 15: Do you agree with the following preliminary appraisal "the option of maintaining the concept of a single sponsor, may be preferable provided that it is clarified that the 'responsibility' of the sponsor is without prejudice to the (national) rules for liability; and it is ensured that the regulatory framework for clinical trials in the EU is truly harmonised? Please comment.

The AEMPS considers that the Directive is not clear in defining the requirement of a single sponsor at the EU level. In case the legislator would choose this option, the requirement of a single sponsor for the EU should be explicit.

There are many specific MS issues in a clinical trial which should be taken into consideration in order to allow that a clinical trial could be performed according to the same protocol in all MS. This includes knowledge about local language, local insurance, contract and data protection legislation, adequate investigators and sites, etc. A single sponsor could find difficult to gather all this knowledge. In addition to this, national legislation not only specify responsibilities for the sponsor, but also economic sanctions in case of liability. The possibility of having a sponsor per MS should be acceptable, provided that there is transparency about that, and a documented share of

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responsibilities which include the commitment to perform the clinical trial the same way in all participating countries, and how the overall data analysis would be performed.

2.6. Emergency clinical trials

Consultation item no. 16: Do you agree with this appraisal that it could be a viable option in order to address this type of research and bring the regulatory framework in line with internationally-agreed texts? Please comment.

The AEMPS agrees with the objective of enabling the possibility of doing clinical trials in emergency situations in the EEA.

However, the list of requirements is not complete.

Regarding the modalities proposed, we would invite the Commission to integrate the conditions laid down by article 5 of the CTD and to take into account the principles of the declaration of Helsinki (article 27), of the convention of Oviedo and of the additional protocol to the convention on human rights and biomedicine, concerning biomedical research and particularly:

- the impossibility of carrying out alternative research of comparable effectiveness on individuals capable of giving consent,
- these individuals must not be included in any study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject (same disease or disorder or condition),
- the research entails only minimal risk and minimal burden.
- Review by the Ethics Committee about the procedure for inclusion and for the continuity of the participants in the CT is ensured.

The Royal Decree 223/2004 has regulated this type of CT in Spain as follows:

«When the clinical trial has special interest for the population in which the research is to be conducted and administration of the investigational medicinal product is justified by reasons of need, a subject may be subjected to a clinical trial without obtaining his/her prior informed consent in the following cases:

a) If there is an immediate serious hazard for the physical or mental integrity of the subject, a suitable alternative treatment is not available in clinical practice and it is not possible to obtain the consent of the subject or his/her legal representative. In this case, whenever the circumstances permit, family members or other persons close the subject should be previously consulted.

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b) If the subject is not capable of making decisions due to his/her physical or mental status and does not have a legal representative. In this case, consent shall be given by family members or other persons close to the subject.»

In both cases, this circumstance and the procedure to be followed must be provided for in trial documentation approved by the Clinical Research Ethics Committee, and the subject or his/her representative shall be informed as soon as possible and shall give their consent to continue in the trial if appropriate.

The subject participating in a clinical trial or his/her legal representative may revoke their consent at any time without giving a reason and without any subsequent responsibility or detriment to the subject.

3. Ensuring compliance with good clinical practices in clinical trials performed in third countries

Consultation item no. 17: Do you agree with this appraisal? Please comment.

The AEMPS agrees with no further comments.

The requirement of registration within the EudraCT database for trials not conducted in any EU country might be waived if the study had been registered in any of the public registries complying with the World Health Organization International Standards for Clinical Trial Registries.

4. Figures and data

Consultation item no. 18: Do you have any comments or additional quantifiable information apart from that set out in the annex to this document? If so, you are invited to submit them as part of this consultation exercise.