Detailed Guidance for the request for authorization 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 of the Network of Coordinating Centres for Clinical Trials (KKS-Network)
Date: 08.09.2009

General comments:
We very much welcome the draft of the revised guidance document for the request for authorization of a clinical trial to competent authorities. We appreciate that the revisions done in the document seem to respond to the fact that the Member States have interpreted the requirements concerning the application in different ways, which was against the objective of the Directive to harmonise the procedures for the conduct of clinical trials with medicinal products between Member States. We believe that the further specification of the requirements set forth in the document and the clearer structure of the revised document will result in a more harmonised approach.

However, to support the harmonisation even further, we recommend to specify also some details of the application which have shown to result in different requirements of the Member States: We recommend e. g. to add specifics with respect to the documentation which has to accompany the request for authorisation as practical experience has shown a lot of different approaches from the Member States. This is especially true for the format and the number of copies of the CTA requested (it should be stated, that one copy is sufficient; this can be an electronic file) and the time periods foreseen for the authorisation procedure in the different Member States. (ECRIN has done a survey on the different requirements in the different countries, which could be made available for illustration).

In the light of the difference in national implementation, we very much appreciate that it has been clearly stated in 1.1. that

> "...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."

It seems to be very important to make this notion legally binding to achieve harmonisation. One way to reach this could be to make the guidance document a regulation. The other way would be to make this sentence part of the revised Directive itself and the other implementing texts. For this, the revision of Directive 2001/20/EC should take place in the foreseeable future and all wording used should be unambiguous to avoid different interpretation by Member States. We would also find it useful to check the other implementing texts with respect to the question whether a clearer specification and description of procedures would be needed.

Detailed comments:
We find it useful that the different paragraphs now start with a repetition of the wording of the directive 2001/20/EC.

We find it also reasonable that the revised guidance document refers to the respective Guidelines / Guidance document for detailed information (e.g. content of the protocol). This avoids sources of error (e. g. concerning the completeness of requirements) associated with duplication of information.

2.1.2 Applicable delays for authorisation, tacit authorisation
The guidance document should refer to a procedure in case different competent authorities in one country need to be involved in the authorisation process because of the specifics of the trial (e.g. including ionising radiation). It should be clearly stated that those additional authorisations form part of the general authorisation process and need to be completed within the time period of maximum 60 days; those involvements should not lead to a delay of the tacit authorisation.

2.1.4.3 Withdrawals
We do not find it necessary that the initial contact has to be made by phone if a request for authorization is withdrawn contact by fax or e-mail followed by a formal letter should be sufficient.

2.1.5. Interface with other authorisation requirements
We would recommend to add information concerning how the applicant and / or the national competent authority should deal with amendments asked for by the ethics committee and / or by the competent authority during the authorisation phase, i.e. how should be dealt with different or even conflicting requests.

2.4. Application form
Normally the sponsor has to sign the application form. In case an applicant signs the application, the applicant needs a sponsor authorisation. This is missing in the guideline.

2.7. Investigational Medicinal Product Dossier
We find the sentence “It should also provide data from non-clinical studies and the previous clinical use of the IMP or justify in the application why information is not provided” not clear enough. Does this refer to information on non-clinical studies and previous clinical use of the IMP or even on the provision of the IMP itself?

3.2. The notion of amendment
We find it very useful that further differentiation has been provided in the guidance concerning what forms an amendment or substantial amendment and what does not. However, we recommend to add a clarification, that the change of an investigator (or involvement of a new investigator) at a trial site who is part of the team will not be regarded as an amendment as long as this is not the principal or coordinating investigator (which of course would be a significant amendment as stated in 3.3.1.).

3.6. Time for response, implementation
In paragraph 3 it is stated 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. “

We would recommend to add a time frame also in the Directive 2001/20/EC itself to make it formally binding.

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