04 Sep 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

Draft revision 3, 2009

COMMENTS FROM:

Name of Organisation or individual
Novo Nordisk A/S

1. GENERAL COMMENTS

	General Comment	Outcome (if applicable)
	In General the term "first administration of a new active substance to humans" could be substituted with "first-human-dose trials".	

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

2. SPECIFIC COMMENTS ON TEXT

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
Section 1.1, 2nd bullet point, p 5	**Comments:** Notifications of proposed substantial ~~proposed~~ amendments; and **Proposed change:**
Section 1.1, , p 5	**Comments:** Last paragraph: As 3rd country trials (included in PIPs) are within scope of Directive 2001/20/EC (amended by the paediatric regulation , and hence this guidance please specify this in the text **Proposed change:** Add text to Foot note 3 "and third countries in accordance with Article 41 of Regulation (EC) No 1901/2006
Section 1.2, , last paragraph, p6	**Comments:** comments to phrasing and terminology **Proposed change:** Please change the wording of this paragraph to use less legal language
Section 2.1.2, 2nd paragraph, p7	**Comments:** **Proposed change:** Please rephrase first line to: The validation of the request for authorisation is included in the 60 days.
Section 2.1.2, 3rd	**Comments:** comments to phrasing and terminology

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
paragraph, p 7	**Proposed change:** Please rephrase first line to: With regards to national competent authorities…
footnote 15, p7	**Comments:** Cf. also Whereas 11 – what is meant with this? **Proposed change:** please change footnote to: Cf. also whereas (11) of Directive 2001/20/EC
2.1.4.2, p 8	**Comments:** It is stated in section 3.2 that changes submitted during the ongoing assessment of the request for authorisation by the national CA (e.g. following the EC opinion) is not considered an amendment. Thus the title of 2.1.4.2 using "amendments" is confusing. In the paragraph only "changes" is used **Proposed change:** in the title of section 2.1.4.2 please use "changes" instead of "amendments"
Section 2.1.6, p 9	**Comments:** The EudraCT request for authorisation form often needs to be translated into local language before submission to a national competent authorities **Proposed change:** It would be highly appreciated if the EudraCT database could be set up to handle other languages than English and Spanish
Section 2.2, p9	**Comments:** Should the applicant inform of any scientific advice in relation to this trial or only relevant scientific advice? **Proposed change:** please speficy
Section 2.3, p10	**Comments:** comments to phrasing and terminology

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
	Proposed change: Please consider to split this section moving the first part up e.g. before section 2.2. The last sentence of Section 2.3 could be moved down to section 2.4.
Section 2.4 (e), p 11	**Comments:** Today Germany and France are requiring a SUSAR listing to be included in the CTA submission. Would SUSAR listing be required for CTA submission to all countries in the future? **Proposed change:** please specify
2.4, parag.2, page 10	**Comments:** It would be helpful if the term "sub-study" could be specified in more detail. The EudraCT application form requires full title, date, version and related objectives of the substudies. It is assumed that there is only 1 protocol and 1 EudraCT number for both the main and the sub-study. **Proposed change:** please specify
2.4, 3rd paragraph, p 10	**Comments:** it is stated that contact person is relevant in one member state only. However, for multinational trials, in the EudraCT application form, it is the **applicant information** in section C (not the sponsor contact person in section B) which is unique for the member state **Proposed change:** please change "contact person" to "applicant information"
Section 2.6, parag. 4+5, page 14	**Comments:** It is mentioned in the last paragraph that the SmPC for marketed products will be the reference document for the assessment of the expectedness of any adverse reactions. I believe that International Product Safety (IPS) at NN normally base expectedness on the safety part of the CCDS in the PSURs and the CCDS is also what is appended to the IBs. The reason for this is to ensure that the same reference for expectedness is used across regions as the labelling may vary. Furthermore, the safety part of the CCDS may be updated faster than the SmPC with new relevant information. If the sponsor is free to pick any SmPC to be used for common reference, then it may deviate from the labelling in the individual countries/regions and this may cause confusion when it comes to expectedness. Also, the SmPC does not contain detailed information on SUSARs as such. **Proposed change:** Consequently, the safety part of the CCDS may seem more appropriate to use for expectedness than any specific SmPC

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
	Please specify which selection criteria should be used for choosing the one SmPC e.g. worst case scenario, the UK version, the version of the country where the comparator is purchased. Please consider if "should" should be changed to "must" in the line: the sponsor should select one SmPC….
Section 2.7.4, last parag. page 17,	**Comments:** it is stated that the sponsor should "suggest possible mechanisms and the exposure required to produce these". **Proposed change:** This section appears very speculative and may be most appropriate for "first in human clinical trials"
Section 2.8.2, p 18	**Comments:** comments to phrasing and terminology **Proposed change** Please rephrase this section as it is currently unclear
Section 2.8.3, lines 10-13, page 18	**Comments:** It may be very difficult to submit additional non-clinical or clinical data to support the safety of a marketed product for use in e.g. a new patient population. Normally, all relevant and available data will already be in the SmPC and the trial is conducted in order to gain this new information. It is therefore rather difficult to understand what the sponsor is supposed to deliver of additional information. **Proposed change:**"Otherwise, the sponsor……or the new dosing regimen if additional information is available"
Section 2.8.3, p 18	**Comments:**"Possibility to refer to the Possibility to refer to the SmPC" **Proposed change:** Please, correct the title of the section
Section 2.10, last bullet, p 21	**Comments:** The entire Summary Report of the Paediatric Investigation Plan should not be part of the CTA submission. The summary report may not reflect the PDCO position and recommendations as it includes the initial comments from the EMEA-coordinator/rapporteur/peer-reviewer. The PDCO Discussion and Request for Modification of the PIP is included as the last part of the Summary Report and we suggest that this part is to be appended to the CTA and not the entire Summary Report.

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
	Proposed change: The agreed/approved PIP and the opinion of the Paediatric Committee and the decision of the EMEA must be submitted
Section 3.2, p 22	**Comments:** It is stated that submission of documentation during the ongoing assessment to the EC is not considered an amendment (e.g., following the opinion of the national competent authority). This is inconsistent with the text in Section 2.1.4.2 where it is stated it is considered an amendment and that it will re-start the timeframe for authorisation **Proposed change:** please clarify
Section 3.2, p 22	**Comments:** The annual update of the IB, if not considered as substantial amendment should it be reported to HAs/IEC (yes/no, i.e.: together with annual reports,...). **Proposed change:** Please specify
Section 3.2, p 22	**Comments:** last paragraph - I understand that a change of sponsor trial coordinator is to be considered as non-substantial amendment. However, it affects the information in the CTA, please clarify how it should be reported. Practice has been to provide the national CA with an updated EudraCT CTA with this information.Please specify, if it is not an amendment, why it should be transmitted to the CA (we assume, -as it affect the EudraCT CTA) **Proposed change:** suggest to change text in last paragrap to: (after "remains identical) A revised copy of the Eudract application form incorporating these changes should be transmitted to the national competent authorities of the member state concerned as soon as possible
Section 3.2, p 22	**Comments:** last paragaph - Please, confirm that it is not required to state the name of the monitors in the CTA/protocol, so that a change of CRA may not lead to any amendment. **Proposed change:** please specify
Section 3.3.1: Page 23	**Comment:** Please consider to divide the section one for substantial amendments and one for non-substantial amendment. The same applies for 3.3.2 and 3.3.3

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
3.5, first paragraph, p 25	**Comments:** The notification form referred to in vol 10, states in section K.2/K.3 that the applicant of the request should sign the form. This includes a reference to C.1, but it is not specified that C.1 of the EudraCT CTA is meant (where the applicant information for the individual member states is given). Section C.1/C.2 of the notification form contains details on the sponsor/legal representative. **Proposed change:** in section K.1 of the notification form please rephrase to: (as stated in section C.1 of the EudraCT application form)
Section 3.6, p 27	**Comments:** Appreciated that the guideline includes a timeline for CA review of Substantial Amendments **Proposed change:** N/A
Section 4.3, p 31	**Comments:** Please, specify if any time limit to send the clinical trial summary report (1 year?) after notification of the end of the trial. The communications from the commission referenced in the paragraph, state 1 year for non-paediatric clinical trials and 6 months for paediatric trials. It says that the summary report **can** be submitted the end of trial notification, but a more clear-cut definition would be helpful. 6 months for paediatric trials is a very short timeline. **Proposed change:** please specify the timelines
Attachment 1 to 3	**Comments:** Would highly recommend that the CTD numbering structure is implemented for CTA's **Proposed change:**
Attachments	**Comments:** The current guideline has included attachments regarding specific requirements for the different member states. Will a similar attachment be included in this guideline or would the requirements be the same in all member states?

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555

Section No + Paragraph No + Page No	Comment and Rationale; proposed changes
	Proposed change: please specify

Novo Nordisk A/S
Novo Allé
2880 Bagsværd
DENMARK
Tel: +45 4444 8888
Fax: +45 4449 0555