31 August 2010

# Submission of Comments on Draft Clinical Trials Guideline "HARMONISED REQUIREMENTS FOR NON INVESTIGATIONAL MEDICINAL PRODUCTS IN CTA SUBMISSIONS (SANCO/C/8/SF/dn D(2010) 326199)"

## Comments from:


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# 1. General comments

| General comments | Outcome (if applicable) |
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| EuropaBio welcomes the opportunity to input into the European Commission consultation on the draft guidance regarding the requirements for non-investigational medicinal products (NIMPs) in clinical trial authorisation (CTA) submissions.<br><br>EuropaBio welcomes the development of guidance which aims at harmonising the dossier requirements for NIMPs used in clinical trials. The draft guidance provides specific guidance on the regulatory expectations for these products within Europe.<br><br>There should be greater clarity on the expectations in respect of products that are not supplied by the sponsor, but provided as background therapy by the investigator site. There is concern among member companies that the sponsor should not be responsible for ensuring the quality or reporting adverse reactions related to such products.<br><br>Whilst we are generally supportive of the guideline, we noted some inconsistencies and lack of clarity on some points throughout the document that we would like to see addressed. Particular concerns are highlighted in our comments below.<br><br>**Categories of NIMPs**<br>Sections 3 and 4 of the draft guidance cover four categories of medicinal products which are normally used in clinical trials as NIMPs, namely background therapy, rescue medication, challenge agents and medicinal products used to assess end-points. However, the Annex to the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials* also describes concomitant medicinal products systemically prescribed to the study patients.<br><br>It would be helpful to set out the documentation for all categories of NIMPs in the draft guidance. | |

| General comments | Outcome (if applicable) |
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| **Grouped Approval for Challenge Agents**<br>Attempts should be made to consider developing an approach to permit approval for a particular NIMP to be used across a number of trials. This could be particularly useful for a NIMP being used as a challenge agent in a series of trials. The discussions on the use of and data required for a particular challenge agent could be discussed and agreed in a single procedure ahead of the submission of any CTAs/protocols for the trials. We believe that such an approach would provide the following benefits:<br><br>• Provide the possibility for sponsors to take off the critical path any issues regarding quality and supply of the NIMP because these could be addressed in advance of the clinical trial by obtaining a "NIMP CTA"<br><br>• It would allow a CTA to focus on the specific use in the trial and any possible interactions between the IMP & NIMP<br><br>• It may encourage manufacturers of challenge agents to obtain approval for clinical trial use, which could facilitate the timely conduct of biomarker studies within the EU. | |

## 2. Specific comments on text

| Guideline section | Comment and rationale; proposed changes<br><br>*(If changes to the wording are suggested, they should be highlighted using 'track changes')* | Outcome |
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| Title | ***Comment:***<br><br>We suggest that the guidance covers not only cover CTA submission but also notification of substantial amendments.<br><br>***Proposed change:***<br><br>We suggest rewording the title as follows: "Harmonised requirements for Non investigational Medicinal Product in Clinical Trials". | |
| Cover Page | ***Comment:***<br><br>In the box, "Important notice", the guidance document is referred to as a Q&A.<br><br>***Proposed change:***<br><br>As this is not the case, we suggest replacing "question and answer" by "guidance". | |
| Introduction | ***Comment:***<br><br>It is stated that the responsibilities of the sponsor regarding the quality of NIMPs are set out in Annex 13 to the EU guidelines on good manufacturing practices.<br><br>***Proposed change:***<br><br>NIMPs should not be subject to Annex 13, as they are not IMPs. Otherwise, they would be required to be released by a QP listed on the EudraCT form, included in the IMPD application, and have IMP labelling. This is inconsistent with the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials*. If the product is approved in the EU this would automatically imply compliance with EU GMP requirements. | |

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| General principles | ***Comment:***<br><br>It is stated that the sponsor should provide details of the NIMPs and their proposed use in the trial protocol.<br><br>***Proposed change:***<br><br>This could give the impression that information on the NIMP is only to be included in the protocol, which would be in contrast with the aims of the draft guidance. Alternatively, the term 'clinical trial application' may be used instead of protocol. | |
| Section 3.2.1 | ***Comment:***<br><br>It is stated that justification should be given "if the product is used outside its marketing authorisation". However, according to the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials,* medicinal products used in a way outside its marketing authorisation in a given country are per definition IMPs.<br><br>There is concern about the extent of division among EU Member States on the classification of a given product as an IMP or a NIMP. This could result in increased financial burden and logistical complexity to the conduct of clinical trials in these Member States. It would be helpful to ensure harmonisation on the definition of an IMP and NIMP in all EU countries to avoid confusion and unnecessary paper work. | |
| Section 3.2.2 | ***Comment:***<br><br>We suggest rewording the first bullet point as follows:<br>"Copy of the SmPC ()" in the concerned MS language or, if available, in English | |
| Section 3.2.2 | ***Comment:***<br><br>Second bullet point: "Information on any repackaging and/or relabeling and a list | |

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| | of sites involved".<br><br>It would be helpful to clarify the information requested:<br><br>• How are the repackaging and/or relabeling activities considered?<br>• Which sites need to be documented? e.g. the clinical sites, the GMP sites, the pharmacies?<br>• What about the translation requirements? | |
| Section 3.2.2 | ***Comment:***<br><br>Last bullet point point: "Justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation".<br><br>It would be more appropriate to cover the interaction between the NIMP and IMPs in the IMP dossier. It does not need to be duplicated here. | |
| Section 3.2.3 | ***Comment:***<br><br>We would welcome more details on what 'manufacturer's authorisation' means for NIMP. Is it the one for investigational use or the MP manufacturer's authorisation? | |
| Section 3.2.3 & 4 | ***Comment:***<br><br>'Importer's authorisation'<br><br>It would be helpful to ensure harmonisation of forms and documentation across EU Member States. | |
| Section 3.2.4 | ***Comment:***<br><br>Third bullet point: "acceptable evidence of GMP compliance including the site of batch release by a Qualified Person (QP)"<br><br>We do not believe that batch release site should not be indicated as such, but the | |

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| | location of batch release may not be known. | |
| Section 3.2.4 | ***Comment:***<br><br>Last bullet point: ”justification of the use of the product if there is a comparable product authorised in the concerned Member State but one with a marketing authorisation in a third country is used in the trial<br><br>We would welcome further clarification on what exactly is meant here. It would be reasonable to provide a justification as to why we are sourcing the product from outside the EU and not using the EU-approved product. | |
| Section 3.2.6 | ***Comment:***<br><br>”This information should be included confirmed in the covering letter.”<br><br>***Proposed change:***<br><br>We suggest rewording as follows: “The covering letter should state that the particular brand of the (authorised) NIMP is not specified in the protocol” | |
| Section 4.2 | ***Comment:***<br><br>The ‘one-size-fits-all’ approach to data requirements for challenge agents is inappropriate, given the accepted importance of the role of challenge agents for biomarker studies in drug development.<br><br>Greater consideration of data requirements is needed depending upon the risks associated with different challenge agents. These differences in risks could be based on factors such as mode of application, e.g. a topical capsaicin cream is of a lower risk compared to an agent that needs to be injected in order to invoke the desired response. | |
| Section 4.2.2 | ***Comment:***<br><br>We suggest dividing this section as per previous section: 1) NIMP with MA in another EU MS and 2) NIMP with MA in an ICH country or an MRA country, especially that certain documents are needed when the NIMP is from a non EU | |

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| | country (e.g. QP release certification, import authorisation). | |
| Section 4.2.2 &3 | ***Comment:***<br>We suggest rewording bullet point 4 to improve clarity.<br><br>***Proposed change:***<br><br>Manufacturer's authorisation for EU sites/QP certification for non-EU sites covering the modification or justification for its absence | |
| Section 4.2.4. | ***Comment:***<br><br>"Trial population in line with the previous approved trial"<br><br>We would welcome clarification on the above. Does this mean population with same age, same sex, same indication? | |
| Section 4.2.4 | ***Comment:***<br><br>We suggest rewording bullet point 5 to improve clarity:<br><br>"Confirmation that there were no safety or quality issues arising from the use of the product as NIMP in the previous trial" | |
| 4.2.4 & 5 | **Comment**:<br><br>Re last bullet point:<br>It is feasible that a particular challenge agent may not have been used in a clinical trial for a number of years. In such cases and where the agent has been bought from a third party, it may thus prove impossible to confirm that the product is manufactured and controlled in line with the previously approved trial. We suggest that the bullet is supplemented with a comment stating that where provision of confirmation is not possible, a justification is needed that the source is appropriate for the intended use and it is deemed comparable to previous use. | |
| Section 4.2.5 | ***Comment:*** | |

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| | We suggest rewording bullet point 5 to improve clarity:<br><br>"Confirmation that there were no safety or quality issues arising from the use of the product as IMP in the previous trial" | |
| Section 4.2.6 | ***Comment:***<br><br>Greater flexibility is needed regarding manufacturing data requirements for challenge agents without an MA that have been previously administered to humans. In some cases the challenge agent may have been manufactured by the applicant and, given that small quantities may only be needed, it may not be feasible to manufacture the agent outside of a lab-based environment. Often, challenge agents can be 'borderline' products (e.g. creams, capsaicin, allergens) that, although they invoke a physiological response, have not received a MA. The manufacturing requirements listed in the draft guidance are very onerous in these cases.<br><br>***Proposed change:***<br><br>We suggest adding 'Where comprehensive data on manufacturing (bullets 3-6) can not be provided, applicants should provide information regarding the source of the NIMP and a justification that this source ensures the quality of the NIMP and is appropriate for the intended use' | |
| Section 4.2.6 | ***Comment:***<br><br>For a number of challenge agents that have been used for many years, it is not value added for applicants to provide nonclinical safety evidence. We suggest that nonclinical data is only needed when there is insufficient clinical evidence to support safety for the intended use.<br><br>***Proposed change:***<br><br>We suggest adding "Where there is insufficient efficacy data to demonstrate safety, evidence that existing nonclinical safety data support the use in the proposed trial" | |
| Annex 1 | ***Comment:*** | |

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| | We believe that Annex 1 is somewhat redundant, and will cause more confusion than provide helpful information as regards GMP expectations.<br><br>***Proposed change:***<br><br>We suggest deleting Annex 1, and instead referring to the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials* for GMP requirements. | |