30 August 2010

Submission of comments on Consultation on Clinical Trials: 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

Stakeholder number	General comment (if any)	Outcome (if applicable) *(To be completed by the Commission)*
	We welcome the initiative to create harmonised guidance in an area related to clinical trials in Europe where differing Member State requirements remain. There are, however, a number of aspects of the draft guidance where apparent inconsistencies or a lack of clarity might hinder its effective implementation. These are addressed in the following comments. It should be clear that this guidance applies to all Member States (MS) whether they consider the particular type of study medication described in this guidance as NIMP or IMP. It is bureaucratic and not in the spirit of EU legislation for MS to require sponsors to satisfy different requirements for the same trial.	
	Classification of NIMPs versus IMPs In general, there appears to remain confusion between NIMPS and IMPs in the absence of a formal legal definition of the former. Without a clear definition of NIMP there is a concern (as already happens) that sponsors will be requested to define materials as IMPs where, e.g., they are being used in unapproved indications, or are repackaged, even when a product appears to comply with the examples of NIMPs given in Eudralex Volume 10, Chapter III. This becomes even more complex for multi-centre trials carried out in more than one Member State, as the classification of NIMPs is currently not applied consistently across the EU (as was acknowledged in footnote 7 of the 2006 Commission guideline on "Definition of IMPs and NIMPs"). Consequently, more clarity on how to appropriately classify a compound as IMP or NIMP is needed. In this respect, we support the MHRA initiative to publish on their website the guidance document "Is the product an investigational medicinal product (IMP) or a non-investigational medicinal product (NIMP)?"[1], and would encourage the adoption of similar principles at a European level. In order to improve the overall clarity and user-friendliness of this guidance document, we would also appreciate the addition of a decision tree as an annex.	
	Breakdown between background therapy/rescue medication and challenge agents: No justification is given within the guidance to explain why there is a breakdown between background therapy/rescue medication and challenge agents, and the apparent mis-match of requirements. We recognise that different requirements may have been based on differing potential risks posed by the different product types. For example, giving an agent to provoke a response may inherently be more	

[1] http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014245&RevisionSelectionMethod=Latest

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	risky than using the same compound as rescue medicine (e.g. giving insulin to a healthy volunteer to provoke a blood glucose drop in a clamp study may be more risky than having insulin available to treat a diabetic patient who experiences very high glucose values on a trial). We believe that the overall clarity of the document could be improved by providing a justification for this breakdown. In addition, there are inconsistencies in the different categorisations applied to NIMPs used as background therapy/rescue medications compared to challenge agents. For example, for background therapy/rescue medication, unlike challenge agents, there is no category for NIMPs that have a marketing authorisation but have been 'modified' other than 'repackaged/relabelled' for use in the trial. This and other inconsistencies should be explained or addressed, as there is no obvious reason for them. Furthermore, sections 3 and 4 of this guidance describe four categories of medicinal products which are normally used in clinical trials as NIMPs. However, in the Annex to the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials,* an additional category of "Concomitant medicinal products systematically prescribed to the study patients" is mentioned. If a product falling into this fifth category is still considered to be a NIMP, the requirements should also be described: the requirements should be the same as those for background therapy.	
	<u>Justifications for use of products as NIMPs</u> To avoid differing interpretations at national level, further clarification or examples of the type of information likely to be needed to comply with the requests for justifications for safe and effective use (e.g. if used outside MA or from non-EU country) should be given. Flexibility needs to be retained, however, to allow for consideration on a case-by-case basis. In many cases, a very brief statement (only a few sentences, e.g. supporting that the product is the standard of care) will suffice, and no additional data should be required. A requirement appears in several sections to justify the use of a product from another Member State or ICH/MRA country when there is a comparable product authorised in the concerned Member State. This is an internal decision for companies and is usually related to cost and/or to facilitate logistics (e.g. central sourcing). For ICH- or MRA-country sourced products, the repeated provision of such information in CTAs should not be necessary if the sponsor has justified the safe and effective use of the product. There should be no need to justify a NIMP's use if it is approved in another EU Member State: for IMPs there is no requirement to provide a justification if they are sourced from another MS. In the event that this requirement remains, a short explanation (e.g. that medicinal product is being sourced from one country to facilitate logistics) should be adequate: more detailed information should	

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	not be necessary.	
	<u>GMP Compliance and Quality Requirements</u> Statements relating to the requirements to ensure GMP compliance are unclear, with apparent differences between what is specified within the categories of background therapy/rescue medication and challenge agents, the sub categories within these NIMPs, and with Annex 1. We would welcome clarification that the guidance for NIMPs, unlike the EU Clinical Trials Directive for IMPs, allows for evidence of appropriate GMP without a manufacturer's authorisation (marketed product or IMP) to support manufacture and/or importation (as appears to be the case in point 2 of Annex 1). It is noted that the Introduction points to Annex 13 of EU guidance on GMP for the responsibility of the sponsor regarding quality of NIMPs, and that Annex 13 as quoted below gives some flexibility in assuring 'appropriate quality': "The sponsor should ensure…that they are of appropriate quality for the purposes of the trial taking into account the sources of the materials, whether or not they are the subject of a marketing authorisation and whether they have been repackaged. The advice and involvement of a Qualified Person is recommended in this task." A risk based approach (e.g. ICH Q9) should be considered in specifying the requirements for assurance of quality of NIMPs, and the same/similar quality requirements as an IMP may not therefore be necessitated.	
	<u>"Pre-Approval" for Challenge Agents</u> 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 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 offer the following benefits: 1. 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 "pre-approval". 2. It would allow a CTA to focus on the specific use of the NIMP in the trial and any possible interactions between the IMP & NIMP. 3. 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

Location of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Commission)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Commission)*
2. General Principles, 1st paragraph		Comment: The statement that the sponsor should provide details of the NIMPs and their proposed use in the trial protocol could give the impression that information on the NIMP is **only** to be included in the protocol, which would be in contrast with the remainder of the draft guidance. Proposed change (if any): It should be made clear where the information described in sections 3 and 4 should be placed within the CTA (e.g. cover letter, annex to application form, IMPD etc.).	
2. General Principles, 1st paragraph		Comment: The guideline attempts to differentiate the requirements for NIMPs into categories, based primarily on the NIMP's source and marketing authorisation status. It should be acknowledged, however, that the precise data requirements **within** each of the listed categories will differ depending on the specific NIMP and its function as a medicinal product, and that a risk-based approach will be applied in determining the type and amount of data required. Proposed change: We suggest adding the following text to section 2: "The guideline describes different categories of NIMPs, based primarily on the NIMP's source and marketing authorisation status. It is recognised, however, that the precise data requirements within each of the listed categories will differ depending on the nature and source of the specific NIMP. A risk-based approach will be applied in determining the type and amount of data required in each specific case."	
2. General Principles, 2nd paragraph, last 2 sentences		Comment: Both this draft guidance and the "Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials" state that: "the sponsor should implement a system allowing traceability of medicinal products which allows adequate reconstruction of NIMP movements", and there should be "an evaluation of compliance". We would like to highlight	

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		that this would be problematic if a NIMP is purchased by the investigator or the pharmacy, and no drug accountability is being kept. Proposed change (if any): We suggest amending the relevant wording in both guidances as follows: "the sponsor should ~~implement~~ ensure that a system is in place at the investigator's site ~~allowing~~ to allow traceability of medicinal products, which allows adequate reconstruction of NIMP movements and administration, taking into account the purpose of the trial and trial subjects' safety. It has at least to include a procedure, established with the investigator and, if applicable, with the hospital pharmacy, to record which patients received which NIMPs during the trial ~~with an evaluation of the compliance~~".	
3.2.1 and 3.2.2		Comment: The guidance includes **different** requirements for NIMPs depending on whether they have a marketing authorisation in the concerned Member State or in another Member State. In contrast, Table 1 of the "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial" (CT-1, EudraLex Volume 10, Chapter I) does not differentiate the requirements for IMPs in the same way: IMPs that have a marketing authorisation in **any** Member State are treated equally. See also comment on sections 4.2.1, 4.2.2 and 4.2.3 below. Proposed change (if any): Section 3.2.1 should be renamed "NIMP is a marketed medicinal product in any ~~the concerned~~ Member State". Section 3.2.2 should be deleted.	
3.2.2, 3.2.3 and 3.2.4		Comment: With regard to the requirement for information on repackaging and/or relabeling and a list of sites involved: if there is no repackaging of the NIMP and the site is only involved in relabeling, we do not believe it should be necessary to list the site. This would be more consistent with the requirement under 4.2.2 that requires 'information on any repackaging and list of sites involved'. Proposed change (if any):	

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		In sections 3.2.2, 3.2.3 and 3.2.4,amend as follows: "information on any repackaging ~~and/or relabeling~~ and a list of repackaging sites involved	
3.2.3, 3.2.4 and 3.2.5		Comment: The requirement for an importer's authorisation should be further expanded upon, to indicate, as for IMPs, that this is required from the site at which there is first entry into the EU, not necessarily in every EU country performing the study.	
3.2.3, 4.2.2 and 4.2.3		Comment: A requirement to provide evidence of a product's "regulatory status in the country of origin" appears in several sections. It is not clear, however, what sort of evidence is expected or what is meant by "country of origin" (country of exportation or country of manufacture). Proposed change (if any): The name of the MA-holder and the MA-number should be provided as proof of the existence of an MA. It should be clearly defined that "country of origin" refers to the country of exportation from which the product is sourced for the trial.	
3.2.3, 4.2.2 and 4.2.3		Comment: The term "confirmation of reduced testing" appears in several sections. We suggest that further clarification is provided about what exactly is meant by this. Furthermore, If NIMP is sourced directly from the manufacturer of the medicinal product via a shipping route with a documented chain of custody and/or from a wholesaler that operates in accordance with *Guidelines on Good Distribution Practice of Medicinal Products for Human Use* (94/C 63/03), this chain of custody provides equal or greater control than medicinal products provided to pharmacies or health care facilities (e.g. clinics, hospitals, etc.). As such, analytical testing of products received under these conditions is excessive. Product sourced in accordance with the *Guidelines on Good Distribution Practice of Medicinal Products for Human Use* provides adequate assurance of the integrity of the medicinal product. For challenge agents, it is not likely that the sponsor will be in a position to	

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		perform analytical testing on some materials such as allergens and, whatever the country of origin, reliance on the source will be necessary. This needs to be recognised. Proposed change: Amend the text in Sections 3.2.3, 4.2.2, 4.2.3 as follows: "Confirmation of reduced testing (e.g. identity) by analytical testing or an alternative appropriate method. <u>This requirement may be waived in the case of medicinal products obtained in accordance with Guidelines on Good Distribution Practice of Medicinal Products for Human Use (94/C 63/03).</u>"	
3.2.4 and 3.2.5		Comment: It should be clarified that the manufacturer's authorisation refers to sites that release in the EU, and not the manufacturer in the country of origin.	
3.2.4, last bullet		Comment: For consistency with section 3.2.3, the last bullet point should be revised. Proposed change: "Justification of the use of the product if there is a comparable product authorised in the concerned Member State <u>or another EU Member State</u>, but one with a marketing authorisation in a third country is used in the trial."	
3.2.5, 1st bullet		Comment: Regarding providing documents on quality and manufacturing as per the guideline CHMP/QP/185401/2004, only the section related to the drug product should be required. If the active substance is already approved in the EU, there should be no need to provide the drug substance section again. Proposed change: "documents on <u>drug product</u> quality and manufacturing as per the Guideline […]"	
3.2.5, 2nd bullet (and 4.2.6, last bullet)		Apparently different requirements are specified for background therapy/rescue medication without a marketing authorisation but where the drug substance has been used in a marketed medicinal product (3.2.5) compared to unlicensed challenge agents used as a NIMP where the active moiety has been previously administered to humans (4.2.6). For example, "acceptable evidence of GMP	

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		compliance including site of batch release by QP" compared to "confirmation of the mechanism for ensuring the quality of the product (e.g. QP release)". Proposed change: The requirements should be revised for consistency, or the differences explained.	
3.2.6, 2nd paragraph		Comment: The second paragraph should be reworded to improve clarity and reduce the possibility of differing interpretations of the information required in the cover letter. Proposed change: Suggest rewording as follows: "~~This information should be included confirmed in t~~The covering letter should state that a particular brand of the NIMP(s) is not specified in the protocol. No additional information is required."	
4.2		Comment: The 'one-size-fits-all' approach to data requirements for challenge agents is inappropriate. 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. For example, 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.	
4.2.1, 4.2.2 and 4.2.3		Comment: The guidance includes **different** requirements for NIMPs depending on whether they have a marketing authorisation in the concerned Member State or in another Member State. In contrast, Table 1 of the "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial" (CT-1, EudraLex Volume 10, Chapter I) does not differentiate the requirements for IMPs in the same way: IMPs that have a marketing authorisation in **any** Member State are treated equally. See also comment on sections 3.2.1 and 3.2.2 above. Proposed change (if any):	

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		Section 4.2.1 should be renamed "*NIMP is a marketed medicinal product in <u>any</u> ~~the concerned~~ Member State*". Section 4.2.2 should be renamed "*NIMP is a marketed medicinal product in ~~an other EU Member State, in~~ an ICH country or in a country which has a Mutual Recognition Agreement with the EU.*" Section 4.3.3 should be renamed "*NIMP is a marketed medicinal product in ~~an other EU Member State, in~~ an ICH country or in a country which has a Mutual Recognition Agreement with the EU but has been modified for use in the trial*".	
4.2.2, 4th bullet		Comment: The bullet concerning "acceptable evidence of GMP compliance for the modification" should be deleted from 4.2.<u>2</u>: the following section, 4.2.<u>3</u>, addresses NIMPs that have been modified from the products marketed in other countries.	
4.2.2 and 4.2.3		Comment: Both sections currently apply to NIMP from other EU Member States or ICH/MRA countries, and include requirements for "reduced testing (e.g. identity) by analytical testing or an alternative appropriate method" and for "evidence of its regulatory status in the country of origin". These requirements should only apply to NIMP from ICH/MRA countries – no further testing or evidence should be required for EU-sourced products. This requirement is inconsistent with section 3.2.2. See also comment above on "confirmation of reduced testing" in sections 3.2.3, 4.2.2 and 4.2.3. Proposed change: These sections should not apply to NIMP from other EU Member States (see comment on sections 4.2.1, 4.2.2 and 4.2.3 above). If that comment is not taken into consideration, we suggest adding "(for ICH/MRA products)" to the beginning of the respective bullet points.	
4.2.2 and 4.2.3, last bullet		Comment: For consistency with section 3.2.3, the last bullet point in both sections should be revised. Proposed change:	

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		"Justification of the use of the product if there is a comparable product authorised in the concerned Member State or another EU Member State, but one with a marketing authorisation in ~~another EU Member State,~~ an ICH country or MRA country is used in the trial."	
4.2.4 and 4.2.5		Comment: The requirements for unlicensed NIMP used in previous trials either as a NIMP (section 4.2.4) or an IMP (section 4.2.5) appear to be identical. It would greatly simplify the guidance if the two sections were combined under one heading. In addition, the draft guidance does not include the possibility of using a NIMP with no marketing authorisation that has previously been used in a trial in **another** Member State (4.2.4 and 4.2.5 address only NIMPs previously used in the concerned Member State). It should be permissible to use a NIMP that has previously been used in other MS (see also comments above on sections 3.2.1 and 3.2.2, and 4.2.1 to 4.2.3). Proposed change: Sections 4.2.4 and 4.2.5 should be combined into one section with the following modified title and requirements: "*4.2.4. NIMP has no marketing authorisation but has been authorised or used as a NIMP or an IMP in a previous trial conducted in any Member State by the same sponsor or where a letter of access to the data from the sponsor of the previous trial is available.* Simplified dossier is required containing • *[Include same requirements as 4.2.4, 4.2.5, plus the following additional bullet]* • (for previous trials in another MS) written agreement from the sponsor of the previous trial that the concerned Member State can obtain information from the competent authority of the Member State in which the previous trial was conducted"	
4.2.4 and 4.2.5, last bullet		Comment: 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 prove impossible to confirm	

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		that the product is manufactured and controlled in line with the conditions of the previously approved trial. Proposed change: We suggest that the bullet is supplemented with a comment, as follows: "confirmation that product is manufactured and controlled (including formulation, site of manufacture, quality control and specifications) in line with the conditions of the previously approved trial taking account of both the initial IMP/NIMP dossier and any subsequent amendments. Where provision of such 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."	
4.2.4 to 4.2.6		Comment: If the applicant is not the sponsor of the trial where the NIMP has been previously authorised for use as a NIMP or an IMP, they may not know that the NIMP or IMP has been previously authorised and could not request a letter of access to the data from the sponsor of the previous trial. If this is the type of information that the applicant would be expected to find in the future public domain of the EudraCT database, we suggest providing guidance on how this information could be accessed. See also General Comment on "Pre-approval" for challenge agents.	
4.2.6, 2nd bullet		Comment: For a number of challenge agents where the active moiety has been used for many years, it is not value added for applicants to provide nonclinical safety evidence. We suggest that **nonclinical** data are only needed when there is insufficient **clinical** evidence to support safety for the intended use. Proposed change: "Where there are insufficient clinical data to demonstrate safety, evidence that existing nonclinical safety data support the use in the proposed trial	
4.2.6, bullets 3 to 6		Comment: 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.	

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		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. Proposed change: An additional sentence should be inserted as follows: "Where comprehensive data on manufacturing (bullets 3-6) cannot be provided, applicants should provide information regarding the source of the NIMP and a justification that this source ensures the quality of the NIMP is appropriate for the intended use."	
Annex 1		Comment: Further clarity is sought on what is required to demonstrate that the NIMP is '*Manufactured under national provisions to the principles of GMP and released for use by an appropriately experienced individual'*. Examples of the evidence that could be provided are requested.	
General comment		We encourage the CTFG to use the EU terminology in the guidance for the sake of clarity and harmonisation with other EU guidelines, e.g. 'not authorised' instead of 'unlicensed'.	

Please add more rows if needed.