Comments on:

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION
VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS
HARMONISED REQUIREMENTS FOR NON INVESTIGATIONAL
MEDICINAL PRODUCTS IN CTA SUBMISSIONS
(JUNE 2010)
- DRAFT SUBMITTED FOR PUBLIC CONSULTATION -

Name of Organisation	Country
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1. Specific Comments on Text

Comment number	Chapter	Paragraph/ Section/Line	Page no.	Comment	Proposed change
1	**1. Introduction**	7th paragraph, line1	3	For readability, the last sentence should be completed with examples of categories of medicinal products which are used in clinical trials as NIMPs and for which the submission dossier is detailed in this guideline	This guideline sets out the documentation that should be submitted for the following types of NIMPs: background therapy, rescue medication, challenge agents and medicinal products used to assess end-points.
2	**2. General Principles**	2nd paragraph, line 6	3	"Traceability of medicinal products" It should be emphasized that the traceability has to be ensured even when the products come through the commercial supply chain	End of paragraph: … irrespective whether the sponsor provided the NIMP or whether the commercial supply chain was used.
3	**3.1.1 Background Therapy**	1st paragraph	3	The term "background therapy" should not be limited to the standard therapy for the indication which is the object of the study. Especially in oncology, the background therapy could be a chemo therapy and the object of the study could be the treatment of a side effect, like nausea and vomiting. Here, background therapy and study therapy would target different indications. That situation occurs in any "supportive care" situation.	Widen the scope of background therapy
4	**3.1.2. Rescue Medication**	1st paragraph	3	Rescue medication is frequently provided during wash out periods of clinical trails (before the trial or in between different active treatment periods). In that case, the rescue medication is not based on	Widen the scope of rescue medication and include periods with "no treatment" necessary because of methodological reasons, e.g. study design requirements

				unsatisfactory efficacy of the NIMP but simply connected to the trial design and ethical principles.	
5	**3.2. Dossier Content**		3-5	Example 3.2.1, 3.2.2, 3.2.3 and 3.2.4 do not automatically rule out each other.	Specifying that one of the options is applicable (and not multiple) would avoid confusion.
6	**3.2.1. NIMP as a marketed … member State**	2nd bullet	4	The wording provides possibility for misinterpretation that if a NIMP is used within the terms of the marketing authorization there is no need to cover the interactions in the documentation. The potential for interaction will not depend on the terms of the marketing authorization and no different requirements should apply for that documentation if the NIMP is used within or outside of its marketing authorisation. During the marketing authorization of the NIMP the interaction with the IMP was most probably not considered as the IMP was not known.	"justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorization" without "and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial" and make it a more general requirement to the documentation using both IMP and NIMP to discuss any potential interaction
7	**3.2.2. NIMP is a marketed … EU country.,** **4.2.2. NIMP is a … in another EU MS, ICH country or country with MRA,** **4.2.3. NIMP is marketed…. Modified for the use in the trial**	1st Paragraph	4, 7-8	For multinational clinical trials where the SmPC varies among the member states (so used outside of its national marketing authorization in some member states but not in others) the proposed change would make in many cases unnecessary the submission of a justification of the safe and effective use of the product.	For a multinational trial where the medicinal product to be used in each Member State is the one authorized at national level and the SmPC varies among Member States, the sponsor could choose one SmPC for the whole clinical trial. This SmPC should be the one best suited to ensure patient safety.

8	**3.2.2.** **NIMP as a marketed … EU country**	2nd and 3rd bullet point	4	In order to be clear which sites are meant, the term "manufacturing site" would be more specific (in contrast to investigational site)	Include "manufacturing"
9	**3.2.3.** **NIMP as a marketed …ICH country**	3rd bullet point	4	In order to be clear which sites are meant, the term "manufacturing site" would be more specific (in contrast to investigational site)	Include "manufacturing"
10	**3.2.3.** **NIMP as a marketed …ICH country**	Last bullet point	4	Reduced testing should not be necessary in case the NIMP is manufactured in an ICH country or in a country for which an MRA exists with the EU	Skip last bullet point
11	**3.2.4.** **NIMP is a marketed … in a third country**	3rd bullet point	4	Not all non-ICH or non-MRA countries' regulation uses the term of Qualified Person.	Instead of "acceptable evidence of GMP compliance including the site of batch release by a Qualified Person (QP)" a reference should be made to the Annex 1, page 10
12	**3.2.4.** **NIMP is a marketed … in a third country**	4th bullet point	4	Manufacturer authorisation/importer's authorisation It is not clear whether the slash needs to be interpreted as "or" or "and".	Replace "/" by "or" or "and" (whatever is required)
13	**4.2.2.** **NIMP is a … in another EU MS, ICH country or country with MRA**	6th bullet point	7	"reduced testing" Is this really necessary?	Skip bullet point with reduced testing
14	**4.2.2.** **NIMP is a … in another EU MS,**	Both topics	7 and 8	are different only as the NIMP "has been modified for use in the trial"	Replace in "repackaging/relabeling" as in section 3 Background Therapy/Rescue Medication.

	ICH country or country with MRA and 4.2.3 NIMP ……..use in the trial			the wording “acceptable evidence of GMP compliance for the modification” (4th bullet point) is misleading in 4.2.2. It should have been about repackaging only.	
15	**ANNEX 1**		10	This Annex is attached to the document but not used as reference through the document, only in the General Principles.	To be referred in 3.2.4.

1. General Comments

The challenge agents and medicinal products used to assess endpoints section has a different structure (3.2.2 & 3.2.3 compared to 4.2.2) than the background therapy and rescue medication section which cannot be explained by the different product categories. If these products are all medicinal products there should be no difference in the document requirements of products coming from other EU member states.