EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL
Consumer goods
Pharmaceuticals

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Comments on 'Harmonised requirements for non investigational medicinal products in CTA submissions (June 2010)' (SANCO/C/8/SF/dn D(2010) 32619)

Comments from:

Name of organisation or individual
Christine Marey (Les Laboratoires Servier) chrisitne.marey@fr.netgrs.com

Commission Européenne, B-1049 Bruxelles / Europese Commisie, B-1049 Brussel - Belgium
Telephone (32-2) 299 11 11
E-mail Sanco-pharmaceuticals@ec.europa.eu

1. General comments

General comment (if any)
Labelling of a NIMP is not considered the same in each Member State of the European Union. Therefore we consider that it would be useful to specify in the section 2. General principles that "In the context of NIMP, re-labelling of a marketed product is not considered as a pharmaceutical operation and does not lead to the change of status of NIMP to IMP".
A traceability of NIMPs (as done for IMPs) is requested in the section 2. General principles. It should be specified there that "Information on any repackaging and/or re-labelling and a list of sites involved" are requested (it is only specified in sections 3.2.2 and 3.2.3) due to the need of traceability and identification of each medicinal products administered to clinical studies participants.
In order to simplify the interpretation of this guidance, it could be useful to find the examples of the different NIMPs cited in annex of the *Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (Volume 10, Notice to Applicants)*: examples of rescue medication (ineffective treatment, anticipated adverse reactions, anticipated emergency situation), challenge agents (skin prick test, blood pressure), medicinal products used to assess end-points in the clinical trial (organ function, arterial wall function), concomitant medicinal products systematically prescribed to the study patients (symptom relief), and background treatment (new product for HIV patients and oncology).
A definition of a "Comparable product" (in section 2. General principles or in annex) would be useful as this expression appears in different sections (3.2.2, 3.2.3, 3.2.4, 4.2.2, 4.2.3). Thus, we would like to propose the following definition : "a product with the same indication" and the addition of examples (generic medicines...).
Precise the regulatory expectations following the item "evidence of its regulatory status in the country of origin" in annex, in order to harmonise the requirements between member states and to avoid their multiplication. Moreover, it seems important to complete this item in the sections 4.2.2 and 4.2.3 by the mention "(except for EU countries)" to harmonise the different sections.

2. Specific comments on text

Line number(s) of the relevant text	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
2. General principles (line 3 of the 1st paragraph) Page 3	Comment: We understand that for a monocentric trial it is more relevant, sometimes, to submit a local version of required documents. But in case of multicentric trials, Competent Authorities should accept English version. We would like thus, to insist on the use of English language, as a basis for file preparation. Proposed change (if any): "*To facilitate the preparation of an harmonised dossier, documents submitted to the Competent Authority ~~may be~~ can be submitted in English*"
Section *3.2.1.NIMP is a marketed medicinal product in the concerned Member State* Page 4	Comment: An harmonisation is necessary concerning the version of the SmPC to be submitted: in section 3.2.3 the copy of the SmPC is "*translated as necessary*". This mention is not precised in the other section 3.2.1. It seems necessary to specify the mention "*translated as necessary*" in order to not oblige the submission of a compulsory translated SmPC in English. Proposed change (if any): Add after "*copy of the SmPC*" the mention "*translated as necessary*" in section 3.2.1.
Section *3.2.2. NIMP is a marketed medicinal product in an other EU Member State* Page 4	Comment: An harmonisation is necessary concerning the version of the SmPC to be submitted: in section 3.2.3 the copy of the SmPC is "*translated as necessary*". This mention is not precised in the sections 3.2.2. It seems necessary to specify the mention "*translated as necessary*" in order to not oblige the submission of a compulsory translated SmPC in English. Proposed change (if any): Add after "*copy of the SmPC*" the mention "*translated as necessary*" in section 3.2.2.

Line number(s) of the relevant text	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
Section *3.2.2. NIMP is a marketed medicinal product in an other EU Member State* Page 4	Proposed change (if any): If the item about the traceability of NIMPs, "*Information on any repackaging and/or relabelling and a list of sites involved*", is precised in the section 2. General principles, we can suppress this mention in section 3.2.2.
Sections *3.2.3. NIMP is a marketed medicinal product in an ICH country or a country whis has a Mutual Recognition Agreement (MRA) with the EU* Page 4	Proposed change (if any): If the item about the traceability of NIMPs, "*Information on any repackaging and/or relabelling and a list of sites involved*", is precised in the section 2. General principles, we can suppress this mention in section 3.2.3.
Section 3.2.4 *NIMP is a marketed medicinal product in a third country (not ICH or MRA country)* Pages 5	Comment: It seems necessary to specify the mention "*translated as necessary*" in order to not oblige the submission of a compulsory translated SmPC in English. In the section 3.2.4, there is no mention to a document equivalent to the European SmPC. Proposed change (if any): For harmonisation, add the following part to the section 3.2.4: "*Copy of the document equivalent to the european SmPC (translated as necessary)*"
Section 3.2.4 *NIMP is a marketed medicinal product in a third country (not ICH or MRA country)* Page 5	Comment: The results of non-clinical and clinical studies for marketed products non belonging to the sponsor's portfolio are rarely available. We would like to come back to a justification of the regulatory status of the NIMP, proof of the evaluation of the non-clinical and clinical studies results, proposed in the last draft version released. Proposed change (if any): Suppression of this item "*Results from non-clinical and clinical studies*" in the section 3.2.4. and replacement by "*Justification of the regulatory status in the country of origin*".

Line number(s) of the relevant text	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
Section 3.2.6 *NIMP is defined in the protocol but is not fixed to a particular product* Page 6	Comment: A same kind of safety evaluation should be applied for each kind of submission. Proposed change (if any): Addition of the following item present in the section 3.2.5, "*Justification for the safe and effective use of the product in the trial taking into account any potential interactions between the NIMPs and the IMPs to be used in the trial and if it is used outside of its marketing authorisation*".
Section 3.2.6 *NIMP is defined in the protocol but is not fixed to a particular product* Page 6	Comment: In order to ensure a good compliance to the product defined in the clinical protocol if a particular brand is not specified, the International Non-proprietary Name (INN) should be used to define the type of product to be used. Proposed change (if any): Addition of this sentence at the end of the first paragraph: "*In that case the product should be identified by its INN"*.
Section 3.2.6 *NIMP is defined in the protocol but is not fixed to a particular product* Page 6	Comment: Typographical error Proposed change (if any): Suppression of the word "*confirmed*" in the last paragraph of the section 3.2.6.
Section *4.2.1.NIMP is a marketed medicinal product in the concerned Member State* Page 6	Comment: An harmonisation seems necessary regarding the version of the SmPC to be submitted: in sections 4.2.2 and 4.2.3 the copy of the SmPC is "*translated as necessary*". This mention is not precised in the section 4.2.1. Moreover, concerning product authorized by a Member State of the European Union or ICH country or MRA, a precision is needed concerning the version of the SmPC provided to the competent authority for the different categories of product. It seems necessary to specify the mention "*translated as necessary*" in order to not oblige the submission of a compulsory translated SmPC in English. Proposed change (if any): Add after "*copy of the SmPC*" the mention "*translated as necessary*" in section 4.2.1.

Line number(s) of the relevant text	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
Section *4.2.2.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* Page 7	Comment: It seems important to complete the item "*evidence of its regulatory status in the country of origin*" in the section 4.2.2 to harmonise the different sections. Proposed change (if any): Add the mention "*(except for EU countries)*" after the item "*evidence of its regulatory status in the country of origin*" in the section 4.2.2.
Section *4.2.3. 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* *Pages 7 and 8*	Comment: It seems important to complete the item "*evidence of its regulatory status in the country of origin*" in the section 4.2.3 to harmonise the different sections. Proposed change (if any): Add the mention "*(except for EU countries)*" after the item "evidence of its regulatory status in the country of origin" in the section 4.2.3.
Section 4.2.5 *NIMP is a unlicensed product which has been used as an IMP in a previous trial conducted in the Concerned Member State by the same sponsor where a letter of access to the data from this sponsor is available* Page 8	Comment: In the title of sections 4.2.4 and 4.2.5, the same concept about the letter of access is expressed but with a different wording: 4.2.4 : "*where a letter of access to the data from the sponsor of the previous trial is available*". 4.25 : "*where a letter of access to the data from this sponsor is available*". Proposed change (if any): In section 4.2.5 suppression of ~~"or another sponsor where a letter of access to the data from this sponsor is available"~~ and replacement by " *or where a letter of access to the data from the sponsor of the previous trial is available"*
Section 4.2.6 *NIMP is a unlicensed product where the active moiety has*	Comment: Both items, "*confirmation of the site of the manufacture of the product*" and "*confirmation of the appropriateness of the manufacturing site eg a copy of the manufacturer's authorisation/EU QP declaration/ importer's*

Line number(s) of the relevant text	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***
been previously administered to humans Page 9	*authorisation*)" have a closed meaning. We think it is a repetition. Proposed change (if any): Suppression of the two other items and replacement by "*confirmation of the site of the manufacture of the product and its appropriateness (eg a copy of the manufacturer's authorisation/EU QP declaration/ importer's authorisation)*"
Section 4.2.6 *NIMP is a unlicensed product where the active moiety has been previously administered to humans* Page 9	Comment: We would like a clarification of the last item in the section 4.2.6 "*confirmation of the mechanism for ensuring the quality of the product (eg QP release)*".