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**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 -**

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Date of discussion of draft by the ad-hoc group for the development of implementing guidelines for the “Clinical Trials Directive” 2001/20/EC:	11 May 2010
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**Important notice:** The views expressed in this questions and answers document are not legally binding. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law.

All updates to this questions and answers document are presented and discussed in the “*Ad hoc* group for the development of implementing guidelines for the ‘Clinical Trials Directive’ 2001/20/EC”. This group is chaired by the Commission and is composed of representatives of all EU Member States and EEA contracting parties.

This draft guidance aims at clarifying the dossier-requirements for so-called non-investigational medicinal products.

**The draft document is submitted for public consultation.** Contributions are invited from all stakeholders related to clinical trials. Stakeholders who are not established within the European Union are equally invited to comment.

**Contributions should be sent by e-mail to [sanco-pharmaceuticals@ec.europa.eu](mailto:sanco-pharmaceuticals@ec.europa.eu) on 31 August 2010 at the latest.**

Contributions will be made publicly available on the 'Pharmaceuticals' website of the Commission once the consultation period is over. If you do not wish your contribution to be made public please indicate this clearly and specifically in the submitted documentation. In this case, only an indication of the contributor will be disclosed.

All contributions will be carefully analysed by the Commission. The final version of the detailed guidance is going to build on this consultation.

## 1. INTRODUCTION

A clinical trial may involve medicinal products which are part of the design of a clinical trial while not being an Investigational Medicinal Product (IMP) as defined in Article 2(d) of Directive 2001/20/EC.

Such products are referred to as non-investigational medicinal products – NIMPs.

Examples for NIMPs are provided in the Annex to the *Guidance on Investigational medicinal products (IMPs) and other medicinal products used in Clinical Trials*<sup>1</sup>.

The principles for use of NIMPs to be followed by the sponsor are set out in section 2.8. of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial* (hereinafter 'detailed guidance CT-1')<sup>2</sup>.

The responsibilities of the sponsor regarding the quality of NIMPs are set out in Annex 13 to the EU guidelines on good manufacturing practices.<sup>3</sup>

In order to allow assessment whether sponsors comply with their obligations, section 2.8. of the detailed guidance CT-1 provides that certain documentation shall be submitted with the request for authorisation of a clinical trial.

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<sup>1</sup> EudraLex, Volume 10, Chapter III.

<sup>2</sup> OJ C82, 30.3.2010, p. 1.

<sup>3</sup> EudraLex, Volume 4 (Document reference: ENTR/F/2/AM/an D(2010) 3374).

This guideline sets out the documentation that should be submitted.

## **2. GENERAL PRINCIPLES**

The sponsor should provide details of the NIMPs and their proposed use in the trial protocol. To facilitate the preparation of a harmonised dossier, documents submitted to the Competent Authority may be submitted in English.

The sponsor is responsible for implementing a system to ensure that the trial is conducted and data are generated in accordance with the principles of Good Clinical Practice. To comply with these principles, a trial has to be conducted according to the protocol and all clinical trial information should be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified. In this context, the sponsor should implement a system allowing 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.

Information on the ways in which sponsors can ensure the quality of the NIMP in terms of the appropriateness of the manufacturing site is included in Annex 1.

## **3. BACKGROUND THERAPY/RESCUE MEDICATION**

### **3.1. Introduction**

#### *3.1.1. Background therapy*

This type of medicinal product is administered to each of the clinical trial subjects, regardless of randomisation group, to treat the indication which is the object of the study. Background treatment is generally considered to be the current standard care for the particular indication in the Member State concerned. In these trials, the IMP is given in addition to the background treatment and safety/efficacy are assessed. The protocol may require that the IMP plus the background treatment is compared to an active comparator or to placebo plus background treatment.

#### *3.1.2. Rescue medication*

Rescue medications are medicines identified in the protocol as those that may be administered to the patients when the efficacy of the IMP is not satisfactory, or the effect of the IMP is too great and is likely to cause a hazard to the patient, or to manage an emergency situation.

### **3.2. Dossier content**

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as background therapy or rescue medication.

3.2.1. *NIMP is a marketed medicinal product in the concerned Member State*

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

3.2.2. *NIMP is a marketed medicinal product in an other EU Member State*

Simplified dossier is required containing

- copy of the SmPC (translated as necessary)
- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation/QP certification for non-EU sites] for the repackaging and/or relabelling or a justification for its absence
- 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 an other EU Member State is used in the trial
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

3.2.3. *NIMP is a marketed medicinal product in an ICH country or a country which has a Mutual Recognition Agreement (MRA) with the EU*

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC or local equivalent (translated as necessary)
- information on any repackaging and/or relabelling and a list of sites involved
- acceptable evidence of GMP compliance [manufacturer's authorisation /QP certification for non-EU sites]for the repackaging and/or relabelling or a justification for its absence
- importer's authorisation

- justification for the use of the product if there is a comparable product authorised in the concerned Member State or an other EU Member State but one with a marketing authorisation an ICH /MRA country is used in the trial
- justification for the use of the product if there is no comparable product licensed in the concerned Member State or it is used outside of its marketing authorisation in the ICH/MRA country
- justification for the safe and effective use of the product in the trial, including any potential for interactions between the NIMP and the IMPs to be used in the trial,
- confirmation of reduced testing (e.g. identity) by analytical testing or an alternative appropriate method

3.2.4. *NIMP is a marketed medicinal product in a third country (not ICH or MRA country)*

Full dossier is required containing

- documents on quality and manufacturing as per the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - CHMP/QWP/185401/2004
- results from non-clinical and clinical studies
- acceptable evidence of GMP compliance including the site of batch release by a Qualified Person (QP)
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial taking into account any potential for interactions between the NIMP and the IMPs to be used in the trial and if it is used outside of its marketing authorisation
- 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

3.2.5. *NIMP has no marketing authorisation (is manufactured specially for use in the proposed trial) but the drug substance is contained in a medicinal product marketed in the concerned Member State or an other EU Member State*

Full dossier is required containing

- documents on quality and manufacturing as per the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - CHMP/QWP/185401/2004

- acceptable evidence of GMP compliance including site of batch release by QP
- manufacturer's authorisation/importer's authorisation
- justification for the safe and effective use of the product in the trial

3.2.6. *NIMP is defined in the protocol but is not fixed to a particular product*

In this situation, the product(s) to be used is/are authorised in the Member State in which the trial is being undertaken but a particular brand is not specified in the protocol.

This information should be included confirmed in the covering letter. No additional information is required.

## **4. CHALLENGE AGENTS/ MEDICINAL PRODUCTS USED TO ASSESS END-POINTS**

### **4.1. Introduction**

#### *4.1.1. Challenge agents*

Challenge agents are usually given to trial subjects to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed. They may be substances without a marketing authorisation, however some have a long tradition of clinical use.

#### *4.1.2. Medicinal products used to assess end-points*

This type of NIMP is given to the subject as a tool to assess a relevant clinical trial endpoint; it is not being tested or used as a reference in the clinical trial.

### **4.2. Content of dossier**

The following examples lay out the contents of the NIMP dossier where the NIMPs are used as challenge agents or as medicinal products used to assess end-points.

#### *4.2.1. NIMP is a marketed medicinal product in the concerned Member State*

Simplified dossier is required containing

- copy of the SmPC
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial

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*

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information on any repackaging and list of sites involved
- acceptable evidence of GMP compliance for the modification (including repackaging) - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence
- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- 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 an other EU Member State, ICH country or MRA country is used in the trial

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*

Simplified dossier is required containing

- evidence of its regulatory status in the country of origin
- copy of the SmPC [or equivalent document] translated as necessary
- information (as per chapter 4 of the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - CHMP/QWP/185401/2004) on any modification to the product and list of sites involved
- acceptable evidence of GMP compliance for the modification - manufacturer's authorisation/QP certification (for non-EU sites) or justification for its absence

- justification for the safe and effective use of the product in the trial if it is used outside of its marketing authorisation and taking account of any potential for interactions between the NIMP and the IMPs to be used in the trial
- reduced testing (e.g. identity) by analytical testing or an alternative appropriate method
- importer's authorisation for ICH/MRA marketing authorisations
- 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 an other EU Member State, ICH country or MRA country is used in the trial

4.2.4. *NIMP is an unlicensed product previously authorised for use as a NIMP in a trial conducted in the concerned 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

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences
- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the use of this product in the previous trial
- confirmation that the 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 NIMP dossier and any subsequent amendments

4.2.5. *NIMP is an unlicensed product which has been used as an IMP in a previous trial conducted in the concerned Member State by the same sponsor or another sponsor where a letter of access to the data from this sponsor is available*

Simplified dossier is required containing

- EudraCT number of previous trial
- confirmation that the trial population is in line with that of the previously approved trial or justification of any differences

- confirmation that the dose/duration of dosing does not exceed that of the previously approved trial or justification of any differences
- justification for the safe use of the product in the trial including any potential for interactions between the NIMP and the IMPs to be used in the trial
- confirmation that there were no safety or quality issues arising from the previous trial
- confirmation that the 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 dossier and any subsequent amendments

4.2.6. *NIMP is an unlicensed product where the active moiety has been previously administered to humans*

Simplified dossier is required containing

- rationale for its safe use in the trial including information on the extent of previous human exposure, including any potential for interactions between the NIMP and the IMPs to be used in the trial
- evidence that existing nonclinical safety data support the use in the proposed trial
- information on the composition, method of manufacture and controls applied to the product
- confirmation of the site of manufacture of the product
- confirmation of the appropriateness of the manufacturing site (eg a copy of the manufacturer's authorisation/EU QP declaration/ importer's authorisation)
- confirmation of the mechanism for ensuring the quality of the product (eg QP release)

## **ANNEX 1 EVIDENCE OF APPROPRIATENESS OF THE MANUFACTURING SITE AND MECHANISM FOR CONTROLLING QUALITY OF THE PRODUCT**

Acceptable evidence of the appropriateness of the manufacturing site and the mechanism for controlling the quality of the product includes, but is not limited to, the following

- (1) Manufactured under the provisions of a manufacturer's authorisation for the manufacture of marketed products or IMPs and QP released
- (2) Manufactured under national provisions to the principles of GMP and released for use by an appropriately experienced individual