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**THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN UNION
 VOLUME 10 - GUIDANCE DOCUMENTS APPLYING TO CLINICAL TRIALS
 GUIDANCE ON INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs) AND 'NON
 INVESTIGATIONAL MEDICINAL PRODUCTS' (NIMPs)
 (REV. 1, MARCH 2011)**

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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 Union law.

1. INTRODUCTION

To facilitate the conduct of clinical trials in the Member States of the European Union¹, especially multi-centre clinical trials carried out in more than one member State it is necessary to have a common understanding of the definition of an investigational medicinal product ('IMP').

This document intends to clarify and provide additional guidance on the definition of IMP and to provide specific guidance about the use of non-investigational medicinal products (NIMPs), in accordance with the applicable EU legislation.

This document complements 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 (CT-1)² (‘detailed guidance CT-1’) and the “Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use”³.

2. MEDICINAL PRODUCTS INTENDED FOR RESEARCH AND CLINICAL TRIALS AND INVESTIGATIONAL MEDICINAL PRODUCTS (IMP)

The Community Code relating to medicinal products for human use excludes, in Article 3(3) of Directive 2001/83/EC, "*medicinal products intended for research and development trials*" from its scope of application.

Directive 2001/20/EC defines in Article 2 (d) an IMP as "*a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.*"

It follows that medicinal products with a marketing authorisation are IMPs when they are to be used as the test substance, reference substance or comparator in a clinical trial, provided the requirement(s) in the definition are met.

3. NON-INVESTIGATIONAL MEDICINAL PRODUCTS (NIMPs)

3.1. What is an NIMP?

NIMPs are medicinal products that fall within Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMP as defined in Article 2(d) of Directive 2001/20/EC.

¹ For the purposes of this document, references to the EU, EU Member States or Member States should be understood to include the EEA or EEA contracting States, unless indicated otherwise.

² OJ C82, 30.3.2010, p. 1.

³ EudraLex, Volume 10.

For instance, some clinical trial protocols require the use of medicinal products such as concomitant or rescue/escape medication for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the protocol to induce a physiological response. A list of types of NIMPs, with examples, is contained in Annex 1.

Medicinal products that do not have a marketing authorisation, but prepared in accordance with a magistral formula, i.e. prepared in a pharmacy in accordance with a medical prescription for an individual patient, and medicinal products prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia⁴ and intended to be supplied directly to the patients served by the pharmacy in question, i.e. officinal formula, as referred to in Article 3(1) and (2) of Directive 2001/83/EC may also be an NIMP.

3.2. Requirements for Non Investigational Medicinal Products

The manufacturing of NIMPs *per se* does not fall within

- The rules for manufacturing of medicinal products, as set out in Title IV of Directive 2001/83/EC⁵; or
- The rules for manufacturing of IMPs, as set out in Article 13 of Directive 2001/20/EC, Article 9 of Commission Directive 2005/28/EC, and Commission Directive 2003/94/EC.⁶

However, the safeguarding of the clinical trial subject, in accordance with Article 3 and the objectives of the Directive has to be ensured *inter alia* by guaranteeing the quality and safety of the products and substances used in the trial.

Therefore, section 2.8 of the detailed guidance CT-1 provides for the principal rules for the choice of NIMP.

When NIMPs do not have a marketing authorization in the EU, appropriate GMP requirements foreseen for the safety of the patients should still be applied and the sponsor should ensure that NIMPs are of appropriate quality for the purposes of the trial, taking into account, among other things, the source of the raw materials and any repackaging. To meet the requirements of Articles 3(2) and as referred to in Article 6(3) of Directive 2001/20/EC relating to protection of the trial subject, the same level of quality and safety should be ensured for the NIMPs as for the IMPs used in the trials.

⁴ For reference to acceptable pharmacopoeial monographs see section 1.5 General Considerations — “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials” CHMP/QWP/18540/2004 final which is part of Eudralex Volume 10 of Rules Governing Medicinal Products in the European Union.

⁵ Cf. Article 3(3) of Directive 2001/83/EC.

⁶ An NIMP is not an IMP as defined in Article 2(d) of Directive 2001/20/EC.

This requirement will be fulfilled by applying for these NIMPs the same requirements as provided for the IMPs, in particular, the standards as provided for in Title IV of Directive 2001/83/EC and the requirements established under Articles 13(3) and 15 of Directive 2001/20/EC should be applied.

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, traceability of medicinal products which allows adequate reconstruction of NIMP movements and administration should be ensured taking into account the purpose of the trial and trial subjects' safety. It has at least to include a procedure to record which patients received which NIMPs during the trial with an evaluation of the compliance, where necessary.

NIMPs may be supplied by the sponsor or by the investigator site.

3.3. Documentation requirements in the application dossier

As a general rule, the documentation requirements in the application dossier for IMPs⁷ also apply to NIMPs.

However, there are possibilities for simplified documentation requirements ('simplified dossier') depending on the extent of knowledge of the NIMP. Annex 2 sets out those simplified documentation requirements.

Regarding language requirements for the documentation in the dossier, reference is made to the detailed guidance CT-1.⁸

Within each document, the amount of data might differ. A risk-based approach will be applied in determining the type and amount of data required for each specific case. Existing voluntary cooperation mechanisms between national competent authorities should be used to ensure harmonised application of a risk-based approach on each specific case.

3.4. Adverse reactions related to NIMPs

Regarding safety reporting related to NIMPs, reference is made to the detailed guidance on safety reporting published in Chapter II of EudraLex, Volume 10.

⁷ Cf. section 2.7. of the detailed guidance CT-1.

⁸ Section 2.1.6.

Annex 1 – Types of NIMPs with examples

This section provides guidance on some categories of medicinal products which are normally used in clinical trials as non-investigational medicinal products (NIMPs).

(1) Rescue medication

Description:

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.

Rescue medication allows patients to receive effective treatment, e.g. placebo controlled clinical trials where a standard treatment is available or dose response studies where lower doses might be ineffective. Rescue medications are sometimes called ‘Escape medications’ in protocols. Usually these NIMPs have a MA in the MS and are used according to the authorised conditions.

Examples:

Ineffective treatment - A repeated-dose, randomised, double-blind, placebo-controlled, three-parallel group study performed to evaluate the analgesic efficacy and safety of intravenous acetaminophen as compared with its prodrug (propacetamol) and placebo in patients suffering mild to moderate pain after an orthopaedic surgical operation. Patients were allowed "rescue" patient-controlled intravenous morphine for pain.

Anticipated adverse reactions - A phase III clinical trial trying to assess the efficacy of a new anti-neoplastic IMP. All patients receive a corticoid /antihistamine treatment in order to minimise the appearance of expected adverse reactions;

Anticipated emergency situation - A clinical trial where a new biotechnology product is to be given for the first time to humans. The protocol requires the availability of appropriate medicinal products needed for the treatment of anaphylactic shock.

(2) Challenge agents

Description:

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 MA, however some have a long tradition of clinical use.

Examples:

Skin prick test - Skin prick tests may be used to identify subjects with allergic responses to specific allergens. Dilute solutions are manufactured from extracts of allergens such as pollens, house dust, animal dander and foods. In the skin prick test, a drop of each solution is placed on the person's skin, which is then pricked with a needle. If the person is allergic to one or more substances, he/she has a wheal and flare reaction. This test may be used as part of the inclusion criteria for a clinical trial of a new medicine to control or prevent symptoms from allergic reactions.

Blood pressure - Open-label sensitivity test of blood pressure response to oral tyramine following treatment with an IMP (new MAO inhibitor) in healthy volunteers.

(3) Medicinal products used to assess end-points in the clinical trial

Description:

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.

Examples:

Organ function - PET radiopharmaceuticals are administered to a clinical trial population to measure the function of a certain organ before and after the subject has been given an IMP whose effects in this organ are the primary end-point of the clinical trial.

Arterial wall function - Acetylcholine is administered directly in coronary arteries to evaluate coronary endothelium dysfunction. The test is performed at baseline – before the first administration of an IMP, and at the end of the study, after the treatment period.

(4) Concomitant medicinal products systematically prescribed to the study patients

Description:

This type of NIMP is given to clinical trial participants as required in the protocol as part of their standard care for a condition which is not the indication for which the IMP is being tested, and is therefore not the object of the study.

Example:

Symptom relief - Testing a non-oncologic medication in a cancer patient, where the objective of the clinical trial is to assess the analgesic effect of a new opiate product. The study design would test the opiate versus active comparator for pain control, in patients treated for cancer with the same anticancer treatment in the two groups, regardless of the trial.

(5) Background treatment

Description:

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 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.

The timing of the start of standard care as a background treatment may be different. For instance:

- Subjects may already be taking the standard care medicine(s) when entered into the study, and this treatment would be one of the inclusion criteria; or

- Newly diagnosed subjects may be assigned to the standard care medicines at the same time as they are assigned to the IMP.

The nature of the background medicine(s) will be specified in the protocol e.g. as the standard treatment given according to local clinical practice, by the name of active substances or medicinal products prescribed depending on patient needs and according to the doctor's judgement.

The standard care medicine(s) for a specific indication (recognised standard of care), or a component of the standard care for a particular medical indication, is based on national and international consensus.

Examples:

Development of a new medicinal product for HIV patients who need prophylaxis against cytomegalovirus (CMV) is likely to include patients on standard of care medicine(s) for their primary disease (e.g. antiretroviral medicinal products).

In oncology, patients often receive combination treatments. These may all be approved for the treatment of the disease to be investigated but may not be completely defined in the protocol. For example the development of a new indication for a medicine used in women with breast cancer recently compared that medicine versus observation in patients who had received, regardless of trial, at least four cycles of neoadjuvant or adjuvant chemotherapy and were allowed concurrent hormonal adjuvant therapy. In this case that medicine would be considered an IMP and the neoadjuvant or adjuvant chemotherapy and hormonal therapy products would be NIMPs.

ANNEX 2 – SIMPLIFIED DOCUMENTATION REQUIREMENTS FOR NIMPs IN THE APPLICATION DOSSIER ('SIMPLIFIED DOSSIER')

1) Simplified dossier in view of marketing authorisation (MA) status:

	NIMP is an authorised medicinal product in a EU Member State	NIMP is an approved medicinal product in an ICH country or a country which has a Mutual Recognition Agreement with the EU ('MRA country')	NIMP is an approved medicinal product in a third country not being an ICH or MRA country	NIMP has no marketing authorisation but the drug substance is contained in a medicinal product authorised in an EU Member State	NIMP is an unauthorised product where the active moiety has been previously administered to humans
Justification of choice of NIMP in view of the 'cascade' set out in §93 of detailed guidance CT-1	X, if MA in another EU Member State	X	X	X	X
Copy of the SmPC ⁱ , ⁱⁱ	X	X			
Evidence of regulatory status in the country where the product is approved	X, if MA in another Member State ⁱⁱⁱ	X	X		
Justification for safe and effective use ^{iv}	X, if used outside the MA	X, if used outside the MA	X	X	X ^v
Quality data					
Documents on quality and manufacturing as per EU Guideline ^{vi}			X	X	X ^{vii}
GMP compliance					
NIMP is manufactured in the EU as approved medicinal product or IMP	Manufacturers authorisation	X	X	X	X
	Importers authorisation	X	X	X	X
NIMP is imported	Certification of GMP compliance of manufacturing site by QP or appropriately experienced individual ^{viii}	X	X	X	X
	Results of reduced testing (e.g. identity) by analytical testing or an appropriate method by QP or appropriately experienced individual		X	X	X
In case of repackaging or relabelling	Information of repackaging or relabelling, and list of sites involved	X	X	X	
	Acceptable evidence of GMP compliance ^{ix} for the repackaging or relabelling or a justification for its absence	X	X	X	

2) Other possibilities for simplified dossier requirements:

a) NIMP is defined in the protocol but is not fixed to a particular product (any NIMP used is authorised in the Member State concerned)

In this situation, the product to be used is authorised in the Member State concerned but a particular brand is not specified in the protocol.

This information should be included in the covering letter. The product used should be identified by general means, such as INN. No additional information is required.

b) NIMP is an unauthorised product which has been used as an IMP or NIMP 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 that 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 NIMP 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 dossier and any subsequent amendments.

i If, in multinational trials, the SmPC varies between the Member States, the SmPC which is best suited to ensure patient safety should be chosen.

ii Or local equivalent (in other regions than EU).

iii Not required if NIMP is used as challenge agent or agent to assess endpoints.

iv Including considerations of any potential for interactions between the NIMP and the IMPs used in the trial.

v Including:

- rationale for efficacy and 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;
- where there is insufficient clinical data to demonstrate safety, evidence that existing nonclinical safety data support the use in the proposed trial;
- explanation about the previous administration of the active moiety to humans.

vi Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation concerning Investigational Medicinal Products in Clinical Trials - CHMP/QWP/185401/2004; For biologicals: Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials - EMA/CHMP/BWP/534898/2008.

vii Where comprehensive data on manufacturing can not be provided, applicants should show that the NIMP is appropriate for the use by providing 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.

viii Account should be taken of specific qualifications for certain types of medicinal products, such as radiopharmaceuticals.

ix For EU-sites: manufacturers authorisation; for non-EU sites: certification of GMP compliance by QP or appropriately experienced individual.