Consultation document

Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)

Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use

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This document does not necessarily reflect the views of the European Commission and should not be interpreted as a commitment by the Commission to any official initiative in this area.

1. INTRODUCTION

To facilitate the conduct of clinical trials in the Member States of the European Union[1], 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 IMPs and to provide recommendations about the use of auxiliary medicinal products (AMPs), in accordance with applicable EU legislation.

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

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.

Regulation (EU) No 536/2014 Article 2 (5) defines an IMP as "*a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial*". Further information on IMPs can be found in "The rules governing medicinal products in the European Union" Volume 10 – Guidance documents applying to clinical trials, Clinical Trials Regulation (EU) No 536/2014 Questions and Answers (currently being updated).

It follows that medicinal products with a marketing authorisation are IMPs too when they are to be used as the test product, reference product or placebo in a clinical trial.

3. AUXILIARY MEDICINAL PRODUCTS (AMPs)

3.1. What is an AMP?

AMPs are medicinal products that fall within Article 3(3) of Directive 2001/83/EC, while not falling within the definition of IMPs as defined in Regulation (EU) No 536/2014 Article 2 (5).

Regulation (EU) No 536/2014 Article 2 (8) defines an AMP as "*a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product*".

[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.

For instance, some clinical trial protocols require the use of medicinal products such as rescue medication, challenge agents, medicinal products used to assess end-points in the clinical trial and background treatment. According to the definition, an AMP must first be a medicinal product. Consequently, not all products used for the needs of a clinical trial are AMPs, e.g. some challenge agents are not defined as AMPs because they are not medicinal products. AMPs should not include concomitant medications; medications unrelated to the clinical trial and not relevant for the design of the clinical trial. A list of types of AMPs, with examples, is included in Annex 1 of this document.

Regulation (EU) No 536/2014 Article 2 (10) defines an authorised AMP as "*a medicinal product authorised in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product*".

Only authorised AMPs may be used in a clinical trial unless an authorised AMP is not available in the Union or where the sponsor cannot reasonably be expected to use an authorised AMP. A justification to this effect shall be included in the protocol.

Where there are problems with respect to the availability of authorised AMPs, unauthorised AMPs may be used in a clinical trial in justified cases. The price of the authorised AMP should not be considered as having an effect on the availability of such medicinal products. Subjects should not have to pay for IMPs, AMPs, medical devices used for their administration and procedures specifically required by the protocol, unless the law of the Member State concerned provides otherwise. Member States shall ensure that unauthorised AMPs may enter their territories for the purpose of their use in a clinical trial.

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 pharmacopoeia and intended to be supplied directly to the patients served by the pharmacy in question, i.e. officinal formula, as referred to in Article 61 (5) of the regulation (EU) No 536/2014..

3.2. Requirements for AMPs

Where the AMP is not authorised, or where an authorised AMP is modified while such modification is not covered by a marketing authorisation, it shall be manufactured according to Good Manufacturing Practice (GMP) or to at least an equivalent standard, in order to ensure

appropriate quality. Full GMP equivalent to GMP for IMPs may not be required in these cases but any deviations need to be justified. Appropriate GMP requirements foreseen for the safety of the patients should still be applied and the sponsor should ensure that AMPs 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.

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 (GCP). 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 AMP 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 AMPs during the trial with an evaluation of the compliance, where necessary.

AMPs 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 IMPs also apply to AMPs irrespective their marketing authorisation Regulation (EU) No 536/2014 Annexes I and II set out the requirements of the application dossier for initial applications and substantial modifications, respectively. It should be left to Member States to establish the language requirements for the application dossier. To ensure that the assessment of the application for authorisation of a clinical trial functions smoothly, Member States should consider accepting a commonly understood language in the medical field as the language for the documentation not destined for the subject.

Labelling requirements for both authorised and unauthorised AMPs are set out in Chapter X and Annex VI of Regulation (EU) No 536/2014. The language of the information on the label shall be determined by the Member State concerned. The medicinal product may be labelled in several languages.

3.4. Adverse reactions related to AMPs

Regulation (EU) No 536/2014 Article 46 states, "*Safety reporting with regard to AMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC*", which cover authorized AMPs.-

Regarding unauthorised AMPs, sponsors are not legally required to report serious adverse reactions. However, the sponsor is obliged to keep detailed records of all adverse events which occur in the trial setting, unless the protocol provides differently (Article 41 of Regulation EU 536/2014) . This would also include all adverse events where a causal relationship with an AMP not authorized in the EU is suspected.

Nevertheless, sponsors are highly encouraged to report adverse reactions to the Eudravigilance Database as described in Article 40 (1) of the regulation. While all SAEs and SARs should be included in the annual safety report of the relevant IMP, and non serious adverse events and non serious suspected adverse reactions should be reported in the Clinical Study Report. Further details, also with regard to adverse reactions possible interacting with IMP, please see safety section of the Questions and Answers Paper Version XX.

In addition according to article 53 the sponsor shall notify Member States of all unexpected events which affect the benefit/risk balance of the clinical trial, but which are not suspected unexpected serious adverse reactions (as referred to in Article 42). **Annex 1 – Types of AMPs with examples**

This section provides guidance on some categories of medicinal products which may be used in clinical trials as auxiliary medicinal products (AMPs).

(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 AMPs are authorised AMPs and are used according to the authorised conditions.

Examples:

Ineffective treatment - A repeat-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-neoplasic 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.

Feedback requested:

You are invited to elaborate further on "early escape" procedures.

(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.

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 AMP is given to the subject as a tool to assess a relevant clinical trial end-point; 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) 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 of care or part thereof for the particular indication. In these trials, the IMP is given in addition to the background treatment and safety/efficacy is 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 of care as a background treatment may be different. For instance:

- Subjects may already be taking the standard of 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 of 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 of care medicine(s) for a specific indication (recognised standard of care), or a component of the standard of care for a particular medical indication, is based on a consensus of Member States concerned.

Examples:

Development of a new medicinal product for HIV patients is likely to include patients on standard of care medicine(s) for their primary disease (e.g. antiretroviral medicinal products). In this case the new medicinal product for HIV would be the IMP and the standard antiretroviral treatment would be background treatment.

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 AMPs.