Auxiliary Medicinal Products in Clinical Trials

Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG)

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Changes compared to superseded version:	- Minor editorial changes. Section 3.2 on the documentation required for placebos as pre-medication. - Section 3.3 on the documentation required for unmodified authorised AxMP. Annex 1: - Challenge agents: recommendation only applicable for challenge agents that are medicinal products. - Background treatment: update on the classification IMP vs AxMP if medicinal product is standard of care. Addition of annex 2 with flowchart on labeling requirements

Important notice: This document should be read in combination with the Clinical Trials Regulation (EU) No 536/2014. The information and views expressed in this document may not in any circumstances be regarded as stating an official position of the European Commission or its services. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law. Additional supportive documents can be retrived on Eudralex 10: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en

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1. INTRODUCTION

To facilitate the conduct of clinical trials in the Member States of the European Union[1], especially multi-center clinical trials carried out in more than one Member State, it is necessary to have a common understanding of the definitions and requirements of an investigational medicinal product (IMP) and an auxiliary medicinal product (AxMP) administered to trial participants in clinical trials. These recommendations on AxMP on matters not specifically required by Regulation (EU) No 536/2014 (CTR) should be followed unless justified.

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

Directive 2001/83/EC Article 1(2) defines a medicinal product as:
"(a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological
or metabolic action, or to making a medical diagnosis."

Directive 2001/83/EC Article 3(3) excludes "*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 ", Clinical Trials Regulation (EU) No 536/2014 Questions and Answers[2] .

It follows that medicinal products with a marketing authorisation are also considered IMPs when they are to be used as the test product, reference product or comparator in a clinical trial. Consequently, IMPs fall within Article 3(3) of Directive 2001/83/EC.

3. AUXILIARY MEDICINAL PRODUCTS (AxMPs)

3.1. What is an AxMP?

AxMPs 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).

[1] EU or countries that follow the Legislation (i.e. EEA)
[2] https://health.ec.europa.eu/document/download/bd165522-8acf-433a-9ab1-d7dceae58112_en?filename=regulation5362014_qa_en_0.pdf

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

Examples of AxMPs are medicinal products used as rescue medication, as challenge agents, to assess endpoints in the clinical trial, or as background treatment as outlined in annex 1. Further, the medicinal product should be related to and relevant for the design of the clinical trial, which excludes 'concomitant medication'. As outlined in preamble 54 concomitant medications is unrelated to the clinical trial and not relevant for the design of the clinical trial. Also, authorised diluents, such as saline, are not considered an AxMP if combined with IMP prior to administration. They are then regarded as excipients in the finished IMP and should not be separately registered in CTIS. For further definition and examples, see Annex 1 of this document.

Regulation (EU) No 536/2014 Article 2 (10) defines an authorised AxMP 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 AxMPs may be used in a clinical trial unless an authorised AxMP is not available in the Union or where the sponsor cannot reasonably be expected to use an authorised AxMP (CTR, article 59). Where there are problems with respect to the availability of authorised AxMPs, unauthorised AxMPs may be used in a clinical trial in justified cases. A justification for this shall be included in the protocol. The price of the authorised AxMP should not be considered as having an effect on the availability of such medicinal products (CTR, recital 53).
A justification for the use of an unauthorised AxMP is foreseen for medicinal products that do not have a marketing authorisation, but are prepared in accordance with a magistral formula, i.e. prepared in a pharmacy in accordance with a medical prescription for an individual patient, and/or 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. official formula, as referred to in Article 61 (5) of Regulation (EU) No 536/2014.

For some trial designs it may be necessary to use placebos for premedication. In these cases, these placebo products should be registered in CTIS, and appropriate quality documentation should be uploaded as part of an AxMPD for this placebo product. Furthermore, the blinding and labelling of the marketed product should be outlined in a simplified Auxiliary Medicinal Product Dossier (AxMPD). See also annex I of the CTR for the document requirements.

AxMPs have to be provided free of charge for the trial participant, unless the law of the Member State provides otherwise as defined in Regulation (EU) No 536/2014 Article 92. It should be noted that for some Member States, an exemption could be applied for, with a justification for not providing AxMPs free of charge for the trial participants (e.g. definition of health policy).

3.2. Requirements for AxMPs

Where the AxMP is not authorised, or where an authorised AxMP is modified[3] 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 and the safety of trial participants. For preparation of radiopharmaceuticals used as diagnostical AxMPs refer to Regulation (EU) No 536/2014 Article 61 (5b) and applicable guidelines.

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 non-authorised AxMP transfers and administration should be ensured taking into account the purpose of the trial and trial participants' safety (CTR, article 51). It has to at least include a procedure to record which patients received which AxMPs during the trial with an evaluation of the compliance, where necessary.

3.3. Documentation requirements in the application dossier

As a general rule, the documentation requirements in the application dossier for IMPs also apply to non-authorised AxMPs and authorised AxMPs which are modified while such modification is not covered by the 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.
Registration in CTIS is only mandatory for non- authorised AxMPs and for authorised AxMPs for which such modification is not covered by the marketing authorisation. The documentation requirements set out in sections F (documentation relating to GMP compliance) and G (full or simplified IMPD) of annex I of the CTR apply.

Unmodified authorised AxMPs can be listed in the cover letter. In that case, no SmPC has to be submitted. Unauthorised AxMPs have to be registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) database before they can be added in CTIS. For instructions, please refer to the CTR quick guide for sponsors[4]

Labelling requirements for both authorised and unauthorised AxMPs are set out in Chapter X and Annex VI of Regulation (EU) No 536/2014 and in the Commission delegated regulation (EU) 2022/2239[5]. See annex 2 with a flowchart on labelling requirements.
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] Modifications which affect the product quality and/or GMP requirements.
[4] https://health.ec.europa.eu/document/download/f5ad2a13-4a41-4ada-81a1-2854783c75c0_en?filename=mp_ctr-536-2014_guide_en.pdf
[5] https://eur-lex.europa.eu/eli/reg_del/2022/2239/oj

3.4. Safety reporting requirements for AxMPs

This section applies to safety reporting requirement of adverse events suspected to be related to the AxMP **only** (= adverse reaction to AxMP). In case a suspicion of (or interaction with) the IMP cannot be ruled out for this adverse event the reporting rules for the IMP apply.

Regulation (EU) No 536/2014 Article 46 states, "*Safety reporting with regard to AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC*[6]". Although this article does not distinguish between authorised and non-authorised AxMPs, Directive 2001/83/EC applies only to authorised medical products.

In order to ensure supervision of the clinical trials and trial participants' safety, the same requirements as those provided for the IMP in Regulation (EU) No 536/2014 should be applied with regard to the obligations of the investigators and the sponsors for the collection, recording, management and reporting of adverse events for non- authorised AxMPs.

In this context, the submitted CTA documentation (e.g., the Investigator's Brochure), should contain a reference safety information for the non-authorised AxMP, unless medically and scientifically justified.

The reporting of suspected unexpected serious adverse reactions (SUSARS) related to the non-authorised AxMP should be to the Eudravigilance clinical trial module (EV- CTM) of the Agency (EMA).

All serious adverse reactions (SARs) to the non-authorised AxMP should be included in the line listings of SARs in annual safety report (ASR) of the respective IMP(s) of the clinical trial(s). Any safety issues that arise in the trial should be addressed in the appropriate sections of the ASR, e.g. added to section 10 of the ASR in the format of development safety update report (DSUR) as specified in
ICH E2F. As per ICH E2F[7] guidance, this ASR will also contain all serious adverse events (SAEs) of the clinical trial(s). A separate ASR of the non- authorised AxMP(s) is not required.

All non-serious adverse events and non-serious suspected adverse reactions should be included in the Clinical Study Report.

As per Article 41 of Regulation (EU) No 536/2014, the investigator must record and report all adverse events (including adverse events with a suspected causal association with AxMPs only, irrespective their authorisation status) unless the protocol provides differently.

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[6] Directive 2001/83/EC Article 107 (1):
'Marketing authorisation holders shall record all suspected adverse reactions in the Union or in third countries which are brought to their attention, whether reported spontaneously by patients or healthcare professionals, or occurring in the context of a post-authorisation study….
By way of derogation from the first subparagraph, suspected adverse reactions occurring in the context of a clinical trial shall be recorded and reported in accordance with Directive 2001/20/EC (Regulation EU 536/2014).'

[7] ICH E2F: Development Safety Update Report
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2F/Step4/E2F_St ep_4.pdf

The sponsor is obliged to keep detailed records of all adverse events reported to it by the investigator. In addition, the procedure for reporting of adverse events with suspected causal relationship with an AxMPs should be clearly defined in the protocol.

The safety reporting in relation to the authorised AxMPs should be done in accordance with Pharmacovigilance rules provided in Chapter 3 of TITLE IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorisations of those products. Where an adverse event is suspected to be related only to an authorised AxMP, and does not result from a possible interaction with the IMP, the responsible persons (i.e. the investigator or the sponsor) are encouraged to report the case to the competent authority in the Member State where the reaction occurred or to the marketing authorisation holder of the AxMP but not to both to avoid duplicate reporting. Where made aware of such case, the competent authority or the marketing authorisation holder should apply the guidance provided in the Good Pharmacovigilance Practices Module VI with regard to the management of this type of safety report. While reporting the suspected adverse reaction, the relevant information regarding the CT (i.e. EU CT number) must be included in the report.

A separate ASR of the AxMPs is not required. However, any information relating to (authorised or non-authorised) AxMPs which are relevant to the IMP may be included in the ASR of the IMP.

In addition, irrespective if the AxMP is authorised or not, in accordance with Article 53(1) of Regulation (EU) No 536/2014, 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 of the Regulation (EU) No 536/2014).

Annex 1 – Types of AxMPs with examples

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

(1) Rescue medications

Description:

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

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 AxMPs are authorised AxMPs and are used according to the authorised conditions.

Examples:

Ineffective treatment – A repeat-dose, randomised, double-blind, placebo-controlled, three-parallel group clinical trial 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.

Preventive treatment of 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 should be medicinal products[8] that falls within the definition of an

[8] Challenge agents may also be a product which is not a medicinal product such as a food product or a medical device. These type of challenge agents are outside scope of this recommendation paper. If these challenge agents are used in a clinical trial sufficient information should be provided in the clinical trial application on the quality and safety of the product.

AxMP Challenge agents are usually given to trial participants to produce a physiological response that is necessary before the pharmacological action of the IMP can be assessed. For challenge agents which are medicinal products the required documentation is specified in section 3.3 of this document and should comply with GMP requirements.

Examples:

Skin prick test – Skin prick tests may be used to identify persons 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. The skin prick test product is considered to be an AxMP in a clinical trial because it is being administered to modify a physiological function by exerting an immunological action.

Active substance increasing blood pressure – In an open-label sensitivity test of blood pressure response to oral tyramine following treatment with an IMP (new MAO inhibitor) in healthy volunteers, tyramine would be considered to be an AxMP as it is administered to modify a physiological function by exerting a pharmacological action.

(3) Medicinal products used to assess endpoints in the clinical trial

Description:

This type of AxMP is given to the trial participant 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 radiodiagnostics – PET radiopharmaceuticals are administered to a clinical trial population to measure the function of a certain organ before and after the trial participant has been given an IMP whose effects in this organ are the primary end-point of the clinical trial.

Active substance testing 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 participants, regardless of randomisation group,

a. to treat the indication which is the object of the study or
b. required in the protocol as part of standard care for a condition which is not the indication under investigation and is relevant for the clinical trial design.

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 or to the background treatment only. However, the current standard of care, or parts of it, will not be considered background treatment if it is part of the trial hypothesis. This is the case if the primary or secondary trial objectives include the investigation of interactions with the test product for complimentary effects or possible adverse interactions, or the standard of care treatment is being used as a reference[9] to compare the effect of the test product.
In these cases, the standard of care is considered an IMP itself and not an AxMP.
Examples for inclusion within primary or secondary endpoint e.g.

- long-term efficacy and/or safety of background treatment (where only short term data is available)
- efficacy and/or safety of background in combination with IMP
- biomarkers for background and/or IMP
- pharmacokinetics of background and/or 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. If a specific treatment regimen for standard of care is mandated in the protocol, it should be clearly specified by active substance, ATC group (level 3) or drug product.

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, should be justified in the protocol if there are discrepancies between the clinical practice in Member States concerned, to address potential bias.

Examples:

Development of a new medicinal product for HIV infected patients is likely to include patients on standard of care medicine(s) for their primary disease (e.g. antiretroviral

[9] 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*

medicinal products). In this case the new medicinal product for HIV infection 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 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 the medicine tested would be considered an IMP and the neoadjuvant or adjuvant chemotherapy and hormonal therapy products would be AxMPs.

Testing a non-oncology medication in cancer patients 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* an active comparator for pain control, in patients treated for cancer with the (same) anticancer treatment in the two groups, regardless of the trial.

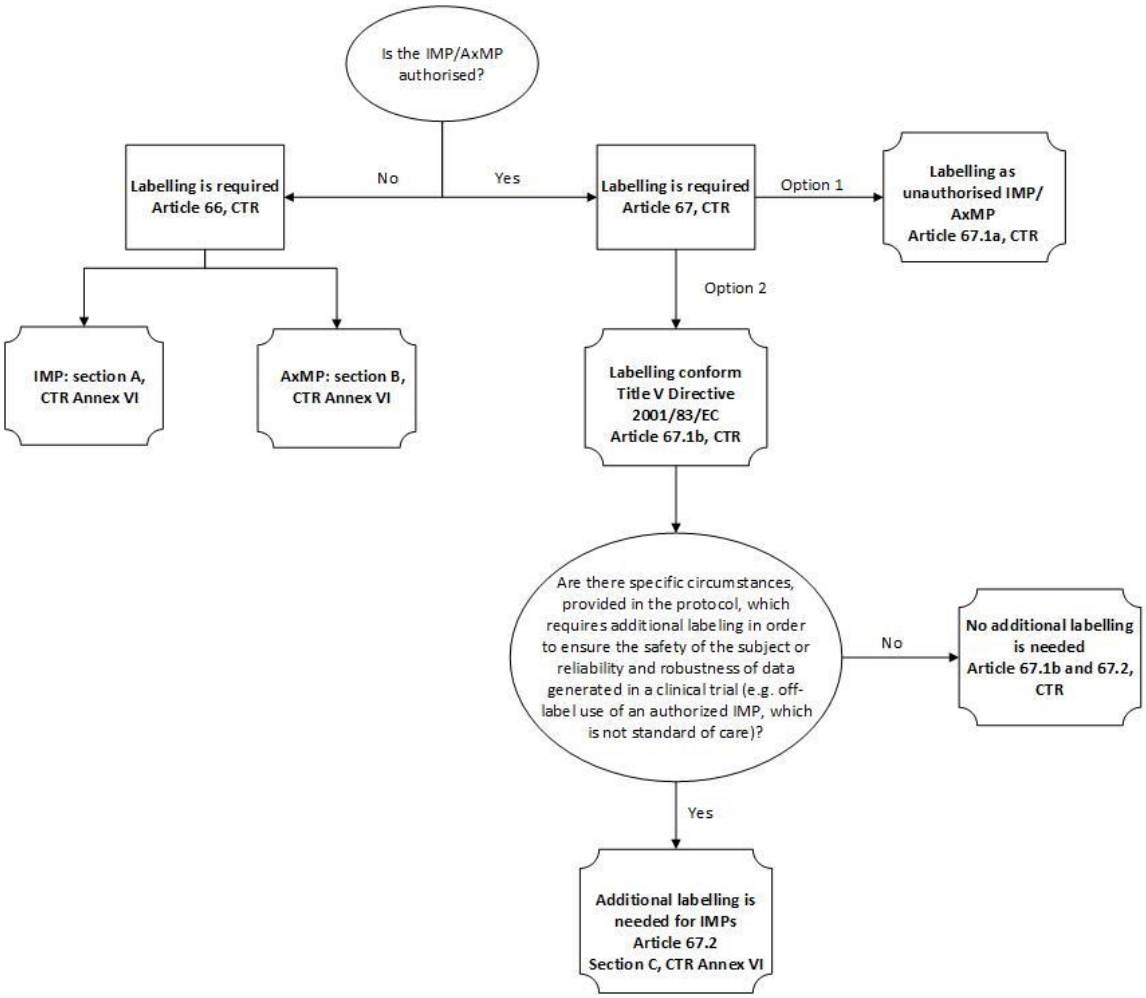
Therefore, the opiate and the active comparator would be the IMP and the oncology medication the AxMPs.

Testing a new laxative IMP medication in patients with chronic pain treated with opioids where the objective of the clinical trial is to assess the laxative effect of the new IMP. The study design would test the laxative *versus* an active comparator, in patients on chronic pain treatment with opioids in the two groups, regardless of the trial.

In this case the laxatives would be IMPs and opioids would be AxMP.

Annex 2 – Flowchart on labelling requirements

Labelling requirements for IMPs and AxMP are set out in chapter X and annex VI of the CTR. A flowchart for labelling under CTR is provided below.



No additional labelling is needed for authorised medicinal products, unless specific circumstances are required in order to ensure subject safety and the reliability and robustness of data generated clinical trials. The specific circumstances should be outlined and justified in the protocol.