

31 Aug 2016

Submission of comments on **Definition of Investigational Medicinal Products (IMPs) and use of Auxiliary Medicinal Products (AMPs)**

Name of organisation or individual

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1. General comments

General comment (if any)

EFPIA welcomes both the updating of this guideline to reflect the new definitions of Investigational Medicinal Products and Auxiliary Medicinal Products arising from Regulation (EU) 536/2014 and the opportunity to provide comments on it.

We would like to highlight the following as our main areas of concern and provide more detailed proposals in the 'Specific Comments on text' section in this response.

- The abbreviation 'AMP' is used elsewhere e.g., in xEVMPD, for 'authorised medicinal product'. In order to avoid confusion we suggest that 'AxMP' be used instead for auxiliary medicinal products.
- Further clarity is required regarding 'challenge agents', especially since it is stated that these may not be auxiliary medicinal products.
- We find the section on GMP requirements in 3.2 is lacking in clarity regarding the manner in which deviations from 'full GMP' may be justified. We suggest it to be clarified and propose that this justification would reside in the local quality system and not be required as part of protocol or in any way subject to regulatory pre-approval.
- It would be useful to be explicit within this guideline that auxiliary medicinal products do not require QP certification based on our understanding from wording of Regulation 536/2014 and the draft Regulation on GMP for IMPs.
- We agree that 'concomitant medicinal products' should not be included within the definition of auxiliary medicinal products, per Lines 76 - 78, but consider that it is still useful to include examples of what falls within this category of products.

In addition, given the stated intent to create an updated Q&A document (Line 52), we would like to suggest the following question with the proposed answer to be added:

Question: Where an IMP is administered using an infusion solution, e.g., saline, which will be an authorised medicinal product in its own right, and the 'placebo' arm just receives the infusion solution without any IMP addition, what is the status of the infusion solution?

Proposed Answer: In this scenario the infusion solution would be regarded as an Auxiliary Medicinal Product. Consequently, it could be provided either by the clinic or the sponsor.

2. Specific comments on text

Line number(s) of the relevant text (e.g. Lines 20-23)	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')
Lines 11-12	<p>Comment: The title does not fully reflect the content of the document as it goes well beyond just providing a definition.</p> <p>Proposed changes: We suggest amending the title to reflect the content of the document, for example to read: 'Auxiliary Medicinal Products and other non-Investigational Medicinal Products in Clinical Trials'</p>
Line 32-33	<p>Comment: This document is providing more than just a common understanding of the definition of an IMP. It is now covering the definition of auxiliary medicinal products and also pointing to the fact that some products administered to subjects in clinical trials may not fall within the definition of either.</p> <p>Proposed change: ... a common understanding of the definitions of an investigational medicinal products (IMP), auxiliary medicinal products (AxMP) and other products administered to subjects in clinical trials which do not fall within either category. Add a sentence: "<u>Suggested content, not specifically required by the regulation, is recommended but not mandatory.</u>"</p>
Lines 54-56	<p>Comment: The inclusion of the term 'placebo' in the context of medicinal products with a marketing authorisation, needs to be clarified and supported by specific examples in the Annex. A product intended to be a placebo <i>per se</i> will not have a marketing authorisation because of the need to demonstrate efficacy. We anticipate that the reference is intended to be in relation to products such as saline infusion solutions which might be administered as part of treatment to a placebo arm of a trial, but would see these as being auxiliary medicinal products in many cases.</p>

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')

(e.g. Lines 20-23)

Proposed change:

We propose a few alternatives to clarify this.

Either:

1) Revert to the wording of the current Volume 10 guidance:

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~~ **comparator** in a clinical trial.

Or:

2) Making the following amendment to the current text:

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

Lines 70-79

Comment:

We find this entire paragraph confusing and it requires clarification. In particular, the situation around when some challenge agents are not medicinal products, and therefore not auxiliary medicinal products, needs to be reflected. Challenge agents can be critical to a trial and will be described in the protocol. We suggest:

- Rewording of this paragraph and adding more extensive coverage in Annex 1 (Section (2) for challenge agents
- Adding new section for coverage of other products administered to trial patients which are neither IMPs nor AxMPs

Proposed change:

~~For instance, some clinical trial protocols require the use of~~ **Examples are** medicinal products **such used** as rescue medication, challenge agents, ~~medicinal products used to assess end-points in the clinical trial and~~ **or** background treatment.

However, the mention of a product in a trial protocol other than as an IMP does not automatically make it an AxMP:

According to the definition, an **AxMP** must first be a medicinal product, **which would exclude** ~~Consequently, not all products used for the needs of a clinical trial are AMPs, e.g.~~ **for example** some challenge agents. ~~are not defined as AMPs because they are not medicinal~~

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	<p>products.</p> <p>Further, the medication should be AMPs should not include Concomitant medications; – medications unrelated to the clinical trial and not relevant for the design of the clinical trial, which excludes ‘concomitant medications’.</p> <p>For further definitions and examples, see Annex 1 of this document. A list of types of AMPs, with examples, is included in Annex 1 of this document.</p>
Lines 92-100	<p>Comment: It is not clear why the statement about subjects not having to pay for medication required by the protocol (lines 95 – 100), and which is copied from Article 92 of the Regulation 536/2014, is included here. We suggest that this paragraph is concluded by the sentence about price not affecting availability.</p> <p>Alternatively, if this statement is to remain, it should be then made clear that this does not mean that these are to be paid for by the trial sponsor. For example, as exemplified in Annex 1, subjects may already be taking background ‘standard of care’ medication at the time of entry into the study and these products would continue to be provided in accordance with the member state healthcare policies before the subject is enrolled in the study, and not by the sponsor.</p> <p>Proposal: 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.</p>
Lines 102-109	<p>Comment/Proposed change: We suggest minor amendment in wording for greater clarity and correct of a typographical error.</p>

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')

(e.g. Lines 20-23)

Proposed change:

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~~ **official** formula, as referred to in Article 61 (5) of the regulation (EU) No 536/2014, **may be classified as AxMP.**

Lines 113-122

Comment:

This paragraph generally requires expansion and greater clarification.

Key points include:

- Clarity of "equivalent standards"
- Release element
- Proposal on where the deviation justification should reside

Proposed change:

~~"... it shall be manufactured according to Good Manufacturing Practice (GMP) or to at least an equivalent standard,~~ **its manufacture should be controlled in order** to ensure appropriate quality **and protection of trial subject safety.** Full **Good Manufacturing Practice (GMP)** ~~equivalent to GMP~~ for IMPs may not be required in these cases but any deviations need to be justified **in the local quality system.** ~~Appropriate GMP requirements foreseen for the safety of the patients should still be applied and~~ **The sponsor should ensure that AxMPs** 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. **AxMPs do not require QP certification."**

Lines 159-163

Comment:

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. Further explanation of the meaning/interpretation of this requirement would be beneficial in the guideline as it can currently be interpreted in multiple ways: 1) Investigator follows standard practices in reporting ADRs he

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	<p>becomes aware of, irrespective if the ADR relates to an AMP or any other product administered to the patient, 2) Sponsor is obliged to systematically collect the causal relationship assessment between the AEs and the AMPs to identify adverse drug reactions for reporting. 3) It remains unclear if the sponsor has the reporting obligation if he is not the Marketing Authorisation Holder of the AMP.</p> <p>Proposed change: We suggesting adding the following clarification: The investigator follows standard practices in reporting Adverse events related to the AMP to the competent authority or the respective MAH.</p>
Lines 163-177	<p>Comment: The paragraphs seem to contain some logical and semantic errors. First paragraph states there is no requirement to report serious related AEs for unauthorized AMP. However, there is a requirement to document all AEs, which would also contain related AEs. All in all, the whole section reads confusing and would benefit of a clearer structure along categorization.</p> <p>Proposed change: We suggest adding a clarification on reporting requirements (and whether related/unrelated are in scope) in the following four categories: SAR, SAE, AR, AE.</p>
Line 219	<p>Comment: We suggest adding some more examples.</p> <p>Proposed change: Additional examples could include:</p> <ul style="list-style-type: none"> • Infusion reactions/cytokine release syndromes with certain forms of immunotherapy • Short acting bronchodilators, e.g., albuterol/salbutamol, for use in the event of ineffective asthma/COPD treatment or excessive reaction to an allergen challenge test

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Line 223 Line 232	<p>Comment: Generally, this section of the Annex should cover the use of challenge agents, both those which fall within the definition of auxiliary medicinal products and those which do not.</p> <p>The skin-prick example utilizes non-medicinal products – and hence is not necessarily an AMP as defined above.</p> <p>Proposed changes: Use this section to cover all challenge agents, both those which fall within the definition of AxMP and those which do not. This would allow coverage of substances without marketing authorisations but with a ‘long tradition of clinical use’ per the current guideline.</p>
Lines 252-254	<p>Comment: Radiopharmaceuticals and contrast agents used for PET or CT scans are usually not provided by the sponsor and are used by radiology/nuclear medicine facilities as standard part of respective assessments. The sponsor doesn’t take measures to have any type of control over these medicinal products (unless it is a special situation with a special agent for a certain trial).</p> <p>Proposed changes: We suggest to delete this example from this section and to indicate that standard contrast agents or radiopharmaceuticals used in radiological or nuclear medicine examinations are not considered AxMP.</p> <p>It is further suggested that a section should be included with this and other examples of agents administered to subjects in clinical trials which are neither IMP nor AxMP.</p>
Lines 260	<p>Comment: The guideline should provide a more detailed background treatment definition with clear inclusion /exclusion criteria in order to avoid any confusion with the definition of concomitant therapies.</p>

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	<p>As concomitant medication is NOT an AxMP, a clear differentiation between concomitant and background medication should be made.</p> <p>Medication required as part of the inclusion criteria to be eligible to participate in the trial should not be considered AxMP.</p> <p>Proposed change: Definition for concomitant medication should be included in the guideline to help clear differentiation of concomitant medications (not AxMP) from background therapies (AxMP).</p>

Please add more rows if needed.

3. Typographical errors and non-technical editorial suggestions

Line number(s) of the relevant text <i>(e.g. Lines 20-23)</i>	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
Line 31	<p>Comment/Proposed change: Suggest the footnote simply be replaced with a reference to EU or countries that follow the Legislation (i.e., EEA).</p>
Line 142	<p>Comment/Proposed change: There should be a full stop between 'authorisation' and 'Regulation' with the latter starting a new sentence.</p>

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	...authorisation. Regulation ...
Line 173	<p>Comment/Proposed change: Delete the 'and' between 'IMP,' and 'non serious' in this line so that the full sentence is as on the right.</p> <p>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.</p>
Line 182	<p>Comment/Proposed change: Move "Annex I...." to the top of the following page as it is the header text for lines 185ff</p>

