2 September 2016

Submission of comments on EC consultation document

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

Comments from:

Name of organisation or individual
AESGP

1. General comments

Stakeholder no. *<to be completed by the Agency>*	General comment (if any)	Outcome (if applicable) *<to be completed by the Agency>*
	The document is in general helpful. So are the details on definitions and many of the examples; it is expected that the paper will add to the clarity and practicability of the new Regulation (EU) No 536/2014.	

2. Specific comments on text

Line No of the first line(s) affected *<e.g. Line 20-23>*	Stakeholder no. *<to be completed by the Agency>*	Comment and rationale; proposed changes *<if changes to the wording are suggested, they should be highlighted using "track changes">*	Outcome *<to be completed by the Agency>*
Line 11-12		**Comments:** The title gives the impression that both IMPs and AMPs are elaborated on exhaustively. This holds, however, not true for IMPs, although the definition of IMPs is highly appreciated. **Proposed change (if any):** Definition and use of Auxiliary Medicinal Products (AMPs) and definition of Investigational Medicinal Products (IMPs)	
Lines 87-100 "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.		**Comments:** It is unclear if an authorised AMP in the EU could also be sourced from a non-EU, however ICH country (e.g. US), where this AMP is also authorised. In global multi-national trials the sponsor might wish to have an authorised AMP only from one commercial source. This should be allowed in the guidance. Furthermore, AMPs authorised in ICH region however not in EU may also be used in clinical trials. **Proposed change (if any):** Only AMPs authorised in the Union or in ICH region may be used in a clinical trial unless an authorised AMP is not available in the Union/ICH region or where the sponsor cannot reasonably be expected to use an authorised AMP. A justification to this effect shall be included in the protocol.	

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Line 96-98 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		**Comments:** In case an AMP is considered as background treatment, and used as standard treatment in the member state, the sponsor will not reimburse it to the patient, but it will rather be taken in charge by national insurance system. **Proposed change (if any):** "…procedures specifically required by the protocol **and not corresponding to standard treatment acknowledged in the member state in case of background treatment**, unless the law …"	
Lines 140 - 142		**Comments:** "As a general rule, the documentation requirements in the application dossier for IMPs also apply to AMPs irrespective their marketing authorisation." **Proposed change (if any):** It would be sensible to define exceptions from this general rule, e.g. for AMPs which are licensed in the country where the clinical trial is taking place, and which are sourced from the local market. A reference to the sourcing of the AMP (e.g. from a pharmacy) might be considered sufficient.	
Line 159 – 162 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		**Comments:** Please explain further the meaning and interpretation of the requirement. Does this imply that the investigator follows standard practices in reporting ADRs he becomes aware of whether to an AMP or any	

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authorized AMPs.-		other product administered to his patients to the competent authority or the respective MAH. Another interpretation of this requirement could be that the sponsor is obliged to systematically collect the causal relationship assessment between the AEs and the AMPs to identify adverse drug reactions for reporting. And it remains unclear if the sponsor has to report to EudraVigilance if he is not the MAH of the AMP. This situation would add an additional burden and complexity to the execution of a clinical trial without adding a benefit to patient health as non-serious adverse events and non-serious suspected adverse reactions should be reported in the Clinical Study Report. **Proposed change (if any):** Addition of: The investigator follows standard practices in reporting Adverse events related to the AMP to the competent authority or the respective MAH.	
Lines 163-177		**Comments:** The two paragraphs contain several logical and semantic errors. First paragraph: No requirement to report serious related AE. However, requirement to document all AE. The sentence: "This would include…" does not make sense, as "all AE" always includes "related AE". Furthermore, it is unclear what is meant by "No requirement to report…": expedite reporting? Reporting in the trial report? (the latter would be in contradiction to the following sentence).	

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		Second paragraph: "Highly encouraged to report adverse reactions…" Again, what is meant by "report"? **Proposed change (if any):** The whole section is confusing and should be clearly structured, to address: Serious or non-serious? Related or unrelated? Which results in four categories: SAR, SAE, AR, AE.	
Line 179 – 183 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).		**Comments:** Please provide further details on the method of reporting, e.g. via the EU Portal, the EudraVigilance Database or any other way of communication.	
Line 219-220		**Comment:** No further "early escape" procedures are conceived.	
Line 232-238		**Comment:** Substances for prick tests are usually unauthorised; they are far from being drugs since they are single substances or excipients. This is reflected in lines 74-76. Contrary to this, examples are given in the annex. For the sake of clarity, it should be stated that no GMP procedures are necessary for challenge agents that are not drugs. **Proposed change:**	

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		Challenge agents are not defined as AMPs, therefore GMP requirements cannot be applied.	
Line 260 -303		**Comment:** Background treatment may vary from patient to patient, which is why not every background medication is provided by sponsors. The extent to which the AMP definition is applicable should be defined. **Proposed change:** Inasmuch background medication is concerned the AMP definition only covers medication that is provided by the sponsor.	

Please feel free to add more rows if needed.