EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<23-Nov-2015>

Submission of comments on Detailed Commission guidelines on GMP for IMPs for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014

Comments from:

Name of organisation or individual
European Qualified Person Association, IMP Working Group (contact: IMPQP@qp-association.eu)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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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 IMP Working Group within the European QP Association very much appreciates the ongoing revision of GMP guidelines for Investigational Medicinal Products for human use in the context of implementation of the Clinical Trial regulation. Representing over 800 QPs specifically managing IMPs we welcome the opportunity to be able to contribute to the public consultation of the "*Detailed Commission guidelines on GMP for IMPs for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014*" (hereinafter referred to as "*detailed Commission guidelines*"). EQPA's comments were filed and should be read in conjunction with the consultation document "*Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures*" (hereinafter referred to as "*Delegated Act*") as well as EudraLex Vol. 4, revised Annex 16 "*Certification by a Qualified Person and Batch Release*", issued on 12 Oct 2015. In general we would like to recommend that the requirements for IMPs and commercial MPs as set forth in revised Annex 16 be clearly delineated, e.g. by introducing clear guidance on the supply chain documentation ("pedigree requirement") available at the stage of certification for the IMP QP either in the "*Delegated Act*" or the "*detailed Commission guidelines*". Concerning the new and significantly more stringent labelling requirements we would like to propose reverting to the well-established Annex 13 requirements and	

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	place particular emphasis on the quality assurance of IRT systems used by the sponsors. We strongly believe that setting harmonized and mutually accepted quality standards for the use of such future-orientated systems will be highly beneficial in the development of new medicines. This could be easily achieved by integrating the principles of EMA's IRT Reflection Paper in the "*detailed Commission guidelines*". Another general comment relates to the terminology around the "expiry date" (use-by date / expiry date (usually meaning that there is not option to extend) / shelf-life / period of use / re-test date). We would highly recommend the harmonized and consistent use of the terminology throughout various relevant IMP guidance (Clinical Trial Regulation, Delegated Act, detailed Commission guidelines, IMPD Guideline, ICH Q1 Guidelines (late phase IMPs in preparation for MAA submission)).	

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>*
90		**Comments:** NIMPs → AMPs The "Notes" section dealing with "Non investigational medicinal products (NIMPs)" has been removed from Annex 13. "Auxiliary Medicinal Products (AMPs)" have been established in the Clinical Trial Regulation. The AMP definition does not cover non-medicinal agents, e.g. challenge agents. **Proposed change:** Clear regulation is required on how to handle non-medicinal agents including challenge agents in future for an EU wide harmonized approach.	
90		**Comments:** NIMPs → AMPs For rare and life-threatening diseases, or in specific therapeutic situations (e.g. Oncology, Immunology, Pediatrics), a treatment regimen based on commercial product is often considered state-of-the-art even though not explicitly approved for the respective indication. In such cases, the commercial product, if used, for example, as background therapy in clinical trials for treatment of the non-approved indication, may be considered AMP, instead of being handled as IMP. However, the medicinal product must be generally accepted as standard	

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		treatment for the individual indication. Such acceptance must be supported by scientific evidence or standard medical practices, and must be reflected in locally or internationally accepted treatment guidelines. Local regulatory acceptance, on handling as AMP, must also be sought. **Proposed change:** Clear regulation would be very helpful to handle such medicinal products as background therapy in clinical trials as AMP in future for an EU wide harmonized approach.	
109		**Comments:** What is the definition for "as close as possible" – timing (as soon as possible after re-constitution) or physical distance (not time related) and what is deemed acceptable? **Proposed change**: Please include clear guidance about acceptable timing and/or distance.	
112		**Comments**: Though not strictly in the scope of these guidelines, the guidelines do nevertheless address issues concerning auxiliary medicinal products, as defined in Article 2(8) of Regulation (EU) No 536/2014, as manufacturing – fully or partially – of those products has to take place according to good manufacturing practice or to at least an equivalent standard	

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		according to Article 65 of said Regulation. • It is not clear what this will mean and the phrase is therefore open to interpretation. • If not strictly "in the scope of these guidelines" why is it applicable? **Proposed change**: Please provide clear guidance.	
179		**Comments:** Premises and equipment are expected to be validated in accordance with EudraLex, Volume 4, Annex 15. However Annex 15 states in section 5.15. "*For the process validation of investigational medicinal products (IMP), please refer to Annex 13*". **Proposed change**: Please clarify.	
183		**Comments:** Primary packing is changed to immediate packaging. Is this change in the wording consistent with other guidelines?	
234		**Comments:** The documentation of the product specification file, including	

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		changes, shall be accessible at the manufacturing site. • The sentence is given is too restrictive and open to interpretation regarding the manufacturing site. • It would make no sense, for example, for the bulk contract manufacturer to have access to the complete PSF (including clinical trial protocol and randomisation codes, etc.). **Proposed change**: Please clarify.	
345		**Comments:** The labelling section (formerly Annex 13 , sec. 26 to 32) goes to Annex VI of the *Clinical Trial regulation* with significant tightening, in particular the deletion to opt-out of some labelling requirements, e.g. use-by date on defined immediate containers such as blister packs or small units such as ampoules (Annex 13, 30) . IRT systems will no longer be allowed to be used for management of use-by dates is perceived as another significant step back (Annex 13, 26 "*The following information should be included in labels, unless its absence can be justified, e.g. use a centralized electronic randomisation system*"). Provided that the IRT system is properly set up and adequately validated this is a crucial tool to manage use-by dates especially in early clinical phases with limited availability of stability data and frequent extension of the shelf life upon availability of new data from (concurrent) stability studies. Other examples are products with inherent short shelf life.	

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		Proposed change: 1) Thus we would like to propose reverting to current Annex 13 requirements, particularly the option to omit details such as use-by date on blister packs and small units such as ampoules (Annex 13, 30) and justified absence of information, e.g. use of a centralised electronic randomisation system (Annex 13, 26). 2) Add clear guidance on requirements for the use of IRT systems, e.g. by adding the principles of the "*Reflection paper on the use of interactive response technologies (interactive voice/web response systems) in clinical trials, with particular emphasis on the handling of expiry dates*", EMA/INS/GCP/600788/2011 (Dec 2013) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500158536.pdf to the "*detailed Commission guidelines*" (in analogy to EMA's QP discretion paper → revised Annex 16, section "unexpected deviations").	
349		**Comments:** Typo **Proposed change:** Annex ~~IV~~ → Annex VI to said Regulation ….	
355		**Comments:** How are the sections concerning labelling of use-by date extension to be interpreted? – is this no longer allowed at	

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		clinical sites? Or is it the intention to cover this by the wording "appropriately trained staff" on condition that a respective quality assurance agreement with the clinical site has been established? If so, please … **Proposed change**: … include clear guidance.	
370		**Comments:** What is meant by "*the approved specification at the time of testing*", is there some hidden meaning? If so, please … **Proposed change**: … include clear guidance.	
420		**Comments**: "*The reference sample should be of sufficient size to perform, on at least two occasions, all critical quality attribute tests as defined ….*" Does the statement "*all critical quality attributes*" - bring back sterility testing? **Proposed change**: Please include clear guidance about the need of reference samples for microbiological testing.	

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441		**Comments:** .. In the absence of an MRA, the qualified person should determine that equivalent standards of good manufacturing practice apply through knowledge of the quality system employed at the manufacturer. This knowledge is normally acquired through audit of the manufacturer's quality systems. In either case, the qualified person may then certify on the basis of documentation supplied by the manufacturer in the third country and document the rationale for certification. • What is the impact for non-EU/non-MRA comparators? Also the section relating to QP release of comparators has been removed. **Proposed change**: Please clarify.	
456		**Comments:** The pedigree requirement in revised Annex 16, section 1.7.2 should be unambiguously clarified and harmonized in the Member States for IMPs. Thus we would like to propose adding either a relevant section in chapter "2.9 responsibilities of the qualified person" in the "*Delegated Act"* **OR** chapter "2.9 release of batches" in the "d*etailed Commission guidelines"* on GMP for IMPs for human use, e.g. line 456 (EQPA prefers the latter).	

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		Rationale: It should be clarified that the pedigree requirement as outlined in the revised Annex 16, including the manufacturing sites of the starting materials and packaging materials, is applicable to commercial medicinal products only. The corresponding QP's declaration concerning GMP compliance of IMPs (http://ec.europa.eu/health/files/eudralex/vol-10/2013-12_qp_template_imp.pdf) starts from the bulk product level. Of course, the selection, qualification, approval and maintenance of suppliers of starting material should be documented as part of the pharmaceutical qualify system to ensure the integrity of the supply chain and protect against counterfeit products. These requirements for IMPs are laid down in the "*detailed Commission guidelines*", line 132 and following. **Proposed change**: Please add either to line 227 "*Delegated Act*" **OR** to line 456 "*detailed Commission guidelines"*, preferred): "The entire supply chain from the investigational medicinal product up to the stage of certification is documented and available for the QP. This should include the manufacturing sites including packaging, labelling and testing of the investigational medicinal product/s and should preferably be in the format of a comprehensive diagram."	

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486		**Comments:** The section on transfers of IMPs from one trial site to another (Annex 13, 47) has been deleted. Does this mean that the site to site transfer is no longer allowed, even in exceptional cases?	
532		**Comments:** The definition for "preparation" does not read well, and the term is not referred to in this document at all. **Proposed change**: Remove definition for "preparation".	
533		**Comments:** All attachments from Annex 13 have been removed. **Proposed change**: We would like to propose reverting to the attachment for optional use of the attachment "*content of the Batch Certificate*" since it clarifies additional requirements for IMP certification beyond Annex 16 and the *MRA for International Requirements for Batch Certification (Part III of EU GMP Guide)*.	

Please feel free to add more rows if needed.