EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<23-Nov-2015>

Submission of comments on Commission Delegated Act on Principles and guidelines on GMP for IMPs for human use and inspection procedures, pursuant to the first 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).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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 "*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*"). EQPA's comments were filed and should be read in conjunction with the consultation document "*detailed Commission guidelines on principles of good manufacturing practice for investigational medicinal products 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*") as well as EudraLex Vol. 4, revised Annex 16 "*Certification by a Qualified Person and Batch Release*", issued on 12 Oct 2015. Specific questions are embedded in the consultation document. A survey was run within the IMP Working Group, the results of which are summarized in section 3.	

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>*
53		**Comments:** Typo **Proposed change**: ~~sue~~ → use	
91		**Comments:** Typo **Proposed change**: ~~internal~~ → initial	
157		**Comments:** We would like to propose to change the wording from 'to identify' to 'to take into account'. **Rationale:** It is the entirety of the manufacturing process and its proper execution that has an impact on safety, data reliability and robustness. The requirement to identify and, consequently, document distinct process steps appears neither feasible nor justified for safeguarding patient safety, data reliability and robustness. This is especially true for early development phases when product knowledge is limited. **Proposed change**: The manufacturer shall take into account the process steps that safeguard the safety of the subject and the reliability and robustness of the clinical trial data generated in the clinical trial.	

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>*
204		**Comments:** Section 2.9 is outlining the responsibilities of the qualified person. We recommend to cross-reference EudraLex 4, revised Annex 16 in this section. **Proposed change**: Please add "The principles of EudraLex Vol. 4, Annex 16 also apply to investigational medicinal products for human use, subject to any difference with the legal provisions and more specific guidance published by the European Commission"	
218		**Comments**: A "*Qualified Person's declaration equivalence to EU GMP for IMPs manufactured in 3rd countries*" is required. Thus, we would like to propose adding a reference to the template. The template itself refers to Art13(3)(b) of Directive 2001/20/EC → revision needed. **Proposed change**: The "*template for the Qualified Person's declaration equivalence to EU GMP for IMPs manufactured in 3rd countries"* as per Commission guideline CT-1, section 2.7.1, paragraph 62 can be found here: http://ec.europa.eu/health/files/eudralex/vol-10/2013-12_qp_template_imp.pdf	

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>*
227		**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 "*detailed Commission guidelines*" on GMP for IMPs for human use, e.g. line 456. EQPA would prefer to add this to the latter. **Rationale:** It should be clarified that the pedigree requirement as outlined in revised Annex 16 including the manufacturing sites of the starting materials and packaging materials is applicable to commercial medicinal products, only. The corresponding QP declaration concerning GMP compliance of IMPs (see above, 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 materials should be documented as part of the pharmaceutical quality 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.	

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>*
		Proposed change: Please add either to line 227 ("*Delegated Act*") **OR** to line 456 ("*detailed Commission guidelines*", preferred by EQPA): "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."	
289		**Comments:** Member States shall carry out inspections of manufacturers located in third countries to ensure that investigational medicinal products imported into the Union are manufactured by applying quality standards at least equivalent to those laid down in Union law. In general the QP has to declare EU GMP compliance of 3rd country IMP manufacturers based on respective audits (see above). If the Member State inspectors ensure equivalent quality requirements, can the QP rely on these inspections for certifying equivalent GMP as well? If yes, please add in line 292… **Proposed change**: Qualified Persons may rely on inspections of third country manufacturers carried out by the Member States when certifying equivalent quality standards.	

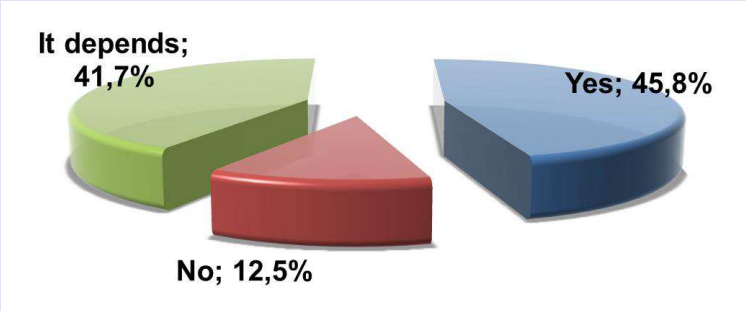
Line No of the first line(s) affected *<e.g. Line 20-23>*	Stakeholder no. *<to be completed by the Agency>*	Comment and rationale; proposed changes *<if changes to the wording are suggested, they should be highlighted using "track changes">*	Outcome *<to be completed by the Agency>*
308		**Comments:** Typo ? **Proposed change:** and ~~lay~~ laboratories → and laboratories	

Please feel free to add more rows if needed.

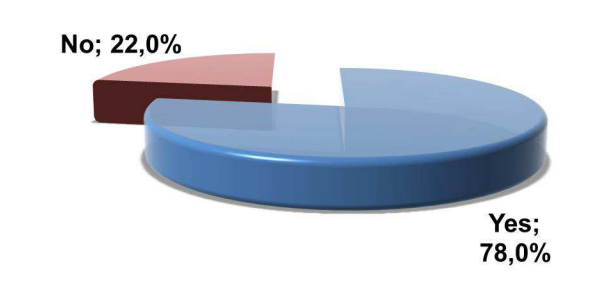
3. Specific questions embedded in the text

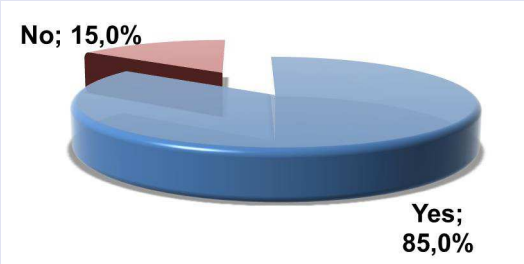
Line No of the first line(s) affected *<e.g. Line 20-23>*	Stakeholder no. *<to be completed by the Agency>*	Comment and rationale; proposed changes *<if changes to the wording are suggested, they should be highlighted using "track changes">*	Outcome *<to be completed by the Agency>*
		A web survey was performed within the IMP Working Group of the EQPA with a total feedback of 26 participants. If not otherwise indicated, percentages are added to the answers we received from the survey. Comments or justification is the consolidated result of feedback received via free text entry fields in the same survey. It reflects the variety and diversity of possible scenarios in the IMP world.	
120		**Question 1a** **Answer**: 100 % - The product specification file is a requirement in Annex 13 and is thus in place. **Comment** We recommend leaving the PSF requirement in the "*detailed Commission guidelines*" section 2.6.3 "as is" → no further introduction in the "*Delegated Act*" required from our perspective.	
125		**Question 1b** **Answer**: 100 % - Yes, product specification files exist for all IMPs in the EU.	

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>*
130		**Question 2** **Answer**: **a) 54 % - Retention for at least five years** after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever period is the longer. Justification: – The retention periods beyond the five years (minimum) should be left for decision by the individual company, e.g. 25 years might not be necessary for small companies with short clinical trials. – There would appear to be no added value in retaining GMP documentation beyond the five years, since, for example, stability studies will have been completed and any quality incidents will have been assessed long before that time. – This would be in line with the practice in place for marketed products in general. **b) 46 % - Retention for at least 25 years** after the end of the clinical trial in line with the retention period of the clinical trial master file. Justification: – In line with the retention time of all documentation regarding clinical trials. – Depends on the type of product. The long retention time is required when, e.g. the product is integrated into the body, in case of gene therapy, human tissue is used as active material in a clinical trial, etc. – In rare cases questions, e.g. from Authorities, have been reported beyond the five years' period.	

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>*
174		**Question 3**  **Answer**: **a) 45.8 % - yes**. Justification: – To rely on proper documentation in order to evaluate the quality of the batch. – To ensure that the product has been analysed as agreed. – May supplement the existing information for IMP available at the importer's site and make sure that defined acceptance criteria when applying test methods to the batch in question are met. **b) 12.5 % - no**. Justification: – It is important to receive the Certificate of Analysis (CoA) at a certain point in time prior to final IMP certification, but not necessarily to accompany each shipment during importation.	

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>
		The IMP bulk batch may be shipped from the 3rd country manufacturer in quarantine status to the sponsor, while analytical control testing is performed at another site. The CoA should in any case carry the appropriate information about the quality control site. – The supply chain integrity as well as samples being representative for the IMP batch in question is both safeguarded by the pharmaceutical quality system. – IMP bulk batches may be ID tested upon goods receipt. – A Quality Assurance Agreement has to be in place to delineate the responsibilities between the 3rd country manufacturer and the sponsor. **c) 41.7 % - it depends**. Justification: – For outsourced batch manufacturing it is also possible that the testing of the batch in question is still ongoing in another country or even in the EU while shipping the product to the sponsor. – It depends on the agreed activities in the Quality Assurance Agreement, e.g. if no QC activities foreseen → then not required, if quality control testing foreseen in 3rd country → yes. – For comparators bought from the market a CoA is not always available and not required. **In any case CoA and CoC must be available as part of the final release documentation at the point in time the QP certification of the finished kit is taking place.**	

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>*
189		**Question 4a**  **78 % - yes**. Justification: – General requirement according to WHO GMPs. – For complaint investigations it is helpful to have the retention kit available for visual examination. – The manufacturer has all the information regarding manufacture of the product. – Each manufacturer has to have the possibility to check the retention sample in case questions arise. – Packaging & labelling manufacturers do not need to keep the reference samples of the incoming bulk product. A sample of the packaged and labelled product only is sufficient. **22 % - no**. Justification: – IMPs are often packaged individually (e.g. in combination sets, kits, etc.)	

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>
		and it would make no sense or even be too costly to keep retention samples of all these. – Some bulk-formulated product has a stability of less than 24 hours. In this case it is necessary to retain a sample, but not for the period that is requested. – The responsibility for retention samples should be delegated to the sponsor within the Quality Assurance Agreement. However, manufacturers retain samples (may not that long) for "safety issues" or in case of discussions. – Use photos in lieu.	
191		**Question 4b**  **85 % - yes**. Justification: – In the event that no retention sample is available, a photo would facilitate / be required for investigations, e.g. in case of complaints. – Photographs provide a good means to demonstrate the real manufacturing steps without incurring a major cost burden.	

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>
		– In case of randomisation and blinding it is more reliable to have pictures of several IMPs than to keep only one sample. In our company all units are "handmade", so it is better to have more pictures in order to prove that there is no difference e.g. between blinded units. – If the control strategy for the products is properly set up and the packaging and labelling process complies with GMP (change management for labels, etc.), the photographs are a useful addition to proof that the process was executed correctly. **15 % - no**. Justification: – Reference samples are stored for the purpose of being analysed should the need arise and must be of sufficient size to perform on at least two occasions all critical attribute tests. – We always rely on authentic retention samples, same logic as for the samples for visual examination. – A photograph would not be sufficient in case of multilingual booklet labels. In this case a sample of the booklet should be kept as well.	
219		**Question 5a** The feedback from the IMP QP Working Group revealed that it is very difficult to answer this question. 50 % of the participants in the survey skipped this question. The following responses represent the high diversity as well as very specific trial scenarios, which individually require the use of third country comparator products.	

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>
		– 22 trials, representing 100 % of the trials authorized (one single feedback company A) – 3 trials, representing 10 % of the trials authorized (one single feedback, company B) – In average up to 5 trials with 3rd country comparator / about 5 % of the trials (one single feedback, company C) – # trials unknown, about 20 % of the trials authorized	
223		**Question 5b** For a detailed overview we divided this question into sub-questions. However, again the response rate was rather low (58 %) and diversity high. **How many non-EU comparators do you use for clinical trials in Europe ?** – 50 % of the trials (one single feedback, company A) – 3 trials (one single feedback, company B) – 4-5 in average (one single feedback, company C) – Few from the USA – None **How many are outside the ICH region ?** – Brazil: 6 trials / around 30 % (one single feedback, company A) – 2-3, eg. Australia, Canada (one single feedback, company C) – None (all other feedbacks)	

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>*
		In which situations do you use non-EU comparators in clinical trials in Europe ? – trials for Brazil, Australia and USA (one single feedback, company A) – a) market availability, b) bioequivalence trials for various countries (one single feedback, company C) – if the comparator is not available in the EU or in a global trial – a risk assessment will be in place (one single feedback, company D) **How many trials do you have using comparators sourced outside the EU (either absolute numbers or estimate percentage) ?** – 50 % of the trials (one single feedback, company A) – Around 20 % (one single feedback, company B) – Very few, e.g. about 5 % of trials (one single feedback, company C) – Only a few trials, exact number not known (majority of feedbacks)	