24 November 2015

Submission of comments on 'Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products 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
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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).

1. General comments:

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EuropaBio welcomes the opportunity to submit these comments and observations on the 'Commission Delegated Act on Principles and guidelines on good manufacturing practice for investigational medicinal products for human use and inspection procedures, pursuant to the first subparagraph of Article 63(1) of Regulation (EU) No 536/2014'. We have consulted with our members and provided below EuropaBio's views in response to the questions asked in the consultation document. In addition, EuropaBio and its members would like to highlight an important point which needs to be addressed in the Delegated Act. The term "manufacturer" is used throughout the consultation document. However it should be recognised that in the majority of cases the sponsor and the manufacturer are not the same legal entity. We believe that the Delegated Act needs to accommodate a range of different practical and contractual arrangements between manufacturers of clinical trial materials and sponsors of clinical trials. Specifically the arrangement between the manufacturer	

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	and the sponsor will ensure alignment with the information submitted by the sponsor in the application dossier for the authorisation of the clinical trial in accordance with Article 25 of Regulation (EU) No 536/2014. The Delegated Act should therefore state that the manufacturer responsibilities may be divided and the contractual agreement between the manufacturer and the sponsor will set out the responsibilities of the parties to ensure adherence to good manufacturing practice for investigational medicinal products. This point is acknowledged in the consultation document "Detailed Commission guidelines on 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" at lines 88-90: "For manufacturers to be able to apply and comply with GMP for investigational medicinal products, co-operation between manufacturers and sponsors of clinical trials is required. This co-operation may be described in a technical agreement." Finally, we noted the new proposed provision with regard to adaptation of good manufacturing practice for ATMPs. In this regard, EuropaBio submitted its response to the consultation on the Commission guidelines on principles	

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	of GMP for ATMPs earlier this month.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(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)*
70-72		It would be helpful to clarify what is expected from the review of manufacturing methods, especially for IMPs. A simple platform that is appropriate for Phase 1-2 clinical development would not be used again in late stage development, and the process may not require periodic review (depending on the dosage form).	
120 – 124 **Question 1a**		**Question 1a:** Would a requirement for a product specification file (a reference file containing, or referring to files containing, all the information necessary to draft the detailed written instructions on processing, packaging, quality control testing, batch release and shipping of an investigational medicinal product) be useful to be introduced? **Answer 1a:** We believe it would not be necessary to introduce a requirement for a product specification file in the Delegated Act. This is already set out in section 2.6.3 of the consultation document "Detailed Commission guidelines on 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".	
125 - 126 **Question 1b**		**Question 1b:** Do product specification files exist for manufacture of all investigational medicinal products in the EU?	

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		Answer 1b: Indeed product specification files do exist; these are created during or after manufacturing and form the basis for assessment of the suitability of certification and release by the qualified person. This is current practice and, therefore, it is not necessary to introduce any additional requirement in this area.	
130-137 **Question 2**		**Question 2**: Different options exist for the retention period of batch documentation: a) Retention for at least five years after the completion or formal discontinuation of the last clinical trial in which the batch was used, whichever is the longer period. b) 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. Please indicate the preferred option with justification. **Answer 2:** It should be noted that manufacturing activities are generally carried out by Contract Manufacturing Organisations, and the sponsor and the manufacturer may not be the same entity, which is often the case for biotech companies. Therefore it is neither useful nor practical to align the retention period of batch documentation to that of the clinical trial master file for which the sponsor has specific responsibilities or the date of completion / discontinuation of the last clinical trial. We recommend a retention period that is calculated starting from	

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		the date of manufacture, which is known to the manufacturer and reflects current practice. We believe that retention for 25 years would be unnecessary and a balance should be struck between 25 (option b) and 5 years (option a). Therefore a retention period of 15 years from the date of manufacture would be appropriate.	
155-156		Comment: We suggest removing "in its entirety" as IMP manufacturing processes are not formally validated in their entirety. Proposed change (if any): Delete "in its entirety"	
174-177 **Question 3**		**Question 3**: Would it be feasible to require that Certificates of Analysis should accompany each shipment of imported investigational medicinal products as a means to ensure that analytical control had been carried out in the third country? Please elaborate your answer to this question. **Answer 3:** We believe such a requirement would neither be feasible nor provide additional value. A qualified person has the legal responsibility to ensure that IMPs used in clinical trials conducted in the EU have been manufactured according to GMP rules and must have arrangements in place that allow an effective supervision. A general requirement that Certificates of Analysis have to accompany every shipment of	

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		IMPs from third countries will not alleviate the QP from his responsibility. In addition, it may be difficult to get Certificates of Analysis for commercial products used as comparators from the wholesaler or distributor from which the material is purchased. In this case, a document confirming the supply chain may be provided.	
189- 190 **Question 4a**		**Question 4a**: Should retention samples also be required to be retained by the manufacturer? **Answer 4a:** No, they should not. The establishment and maintenance of a quality control system under the authority of a person who has the requisite qualifications and is independent of production is already set out in section 2.8 of the consultation document "Detailed Commission guidelines on 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". There is no benefit for the retention samples to be kept by the manufacturer while they are already in possession of the sponsor. Having duplicate samples with the manufacturer as well as with the sponsor may simply be unfeasible for small amounts of IMPs (especially for early phase studies). It would be more appropriate for the sponsor and the manufacturer to establish compliance with this requirement through contractual arrangements.	

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191 - 193 **Question 4b**		**Question 4b**: If only reference samples are required, would a requirement for photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample be useful? Please justify **Answer 4b:** Photos of the investigational medicinal product, the packaging and the labelling to supplement the reference sample may be useful in some cases; for example, for internal purposes and better coordination between company management and researchers. Photos of the final packaging would also be useful as retention samples; for example, to explain how the supplies were packaged.	
219-226 **Question 5a and 5b**		**Question 5a**: In how many clinical trials authorised under the Clinical Trials Directive has Article 13(3)(c) of that Directive been used? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available. **Question 5b**: In how many clinical trials authorised under the Clinical Trials Directive, is the comparator product not authorised in an ICH country (EU, US, Japan, Canada and Switzerland)? Please provide figures both as actual number of trials and as a percentage of the trials authorised, if available. **Answer 5a:** As a trade association, it is difficult for EuropaBio to provide exact figures. However we understand from our members that the percentage of trials where Article 13(3)(c) of the Directive has been used is very small, approx. 3-5% of	

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		clinical trials.	
308		Comment: We suggest replacing “lay” by “contract” laboratories.	
310		Comment: It would be helpful to clarify this statement “Take samples including with a view to independent tests being carried out by an Official Medicines Control Laboratory”.	

Please add more rows if needed.