EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5th November 2013

Submission of comments on "Revised Annex 16 - Certification by a Qualified Person and Batch Release"

Request issued by The European Commission - Health and Consumers Directorate-General, on July 5th, 2013

Comments from:

Name of organisation or individual
E.I.P.G. (European Industrial Pharmacists Group)

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 number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	E.I.P.G. welcomes this Annex 16 revision. Though this draft document is well focused and relevant, it does not give clear references about its application to Investigational Medicinal Products. This draft document correctly introduces distinction between the two terms, *certification* being used to define the QP decision to make the batch available for release and *release* being used to describe the act of making the batch available in the market. However, this distinction is not consistently implemented in the draft, e.g. in points 1.1, 1.4 and 2.3, where only *batch release* is mentioned. Furthermore, given the increasing globalisation of pharmaceutical industry operations, the sharing of responsibilities in the field of batch certification and confirmation between a QP in the EEA and responsible staff in areas where the concept of QP does not exist, is still not addressed with this proposed text. For example, in point 3.4.3. responsibility sharing is addressed within the EEA only.	

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)*
2.3		Section 1.1. makes this Annex applicable to investigational medicinal products (IMP), however, the rest of the text does not take IMP into account, since IMP does not have an MA, but does have certification and batch release. Batch release takes into account different steps compared to the ones used for regular medicinal products. Full text should be reviewed in light of IMP standards, including national IMP legislation.	
2.3 & 2.4		The wording used should be consistent among the different sections throughout the text. For example 'controlling batch release' is used in 2.4. versus 'batch certification' in 2.3.	
2.3.1		The closure of any deviation should also be included	
2.3.2		For the sake of consistency with other sections, the wording 'or equivalent' should be added after 'EU GMP'	
3.1		'Certification can only be performed by a QP of a Manufacturing and Importation Authorisation (MIA) holder named in the MA' The wording 'or equivalent' should be added in order to cover in addition the IMP's.	
3.2		" …and any change to GMP" should be changed to "… and applicable current GMPs".	
3.2		'…any other legal obligation' should be omitted, as it is not related to 'certification' as defined in the Glossary or the reference to "any other legal obligation" should be included in the corresponding definition.	

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3.3		For the sake of consistency in wording used in other sections 'declaration of compliance' should be changed to 'confirmation'	
3.3		For the sake of readability 'QPs who have confirmed compliance of specified steps' should be changed to 'QPs who have given confirmation for specified steps'	
3.3		When different steps of manufacturing are performed at different sites, it should be clarified which site is responsible for the GMP compliance of the API manufacturer. According to point 3.5.9 of this document, it seems that only the final QP would be responsible for this compliance.	
3.4		For medicinal products manufactured outside the EEA, physical importation, certification and batch release are the final stages of manufacturing.' Thus, the wording should be changed to '…certification is the final stage of manufacturing'.	
3.4.5		This point appears ambiguous about what kind or what extent of testing is required. It is proposed to simply define that testing according to the requirements of the MA is required.	
3.4.6		It should be possible to take all samples, and not just sterility samples in the third country, provided that the sampling scheme is justified and the samples are representative of the batch such that subsequent steps do not affect attributes of the batch. Allowing testing to occur in parallel with the transport of the batch keeps batch release cycle times to a minimum and facilitates market availability of products for patients.	

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		The sentence at point 3.4.6 should be changed to: "Sampling of imported product should be representative of the batch."	
3.4.7		Samples for sterility testing should be representative also in case of terminal sterilization (see considerations to the coldest point of the load, at Annex 1, 127b)	
3.4.8		The testing performed on first arrival in EEA is sufficient to guarantee the quality of the batches from the same bulk batch imported subsequently, provided that they are representative for the entire batch and have been shipped under the same conditions. The specification: "…provided that the ID and assay testing are conducted on each occasion within the EEA …" should be deleted.	
3.5.3		It is proposed to replace "register or equivalent document" with "register or equivalent document/electronic system", since typically electronic systems are used rather than paper to record certification.	
3.5.4		After 'EU GMP' the wording 'or equivalent' should be added (see also our comment on 2.3.2. above)	
4.2.6		It is proposed "Repeated audits should be performed …" should be amended to "The frequency and the extent of audits should be defined …" , to better reflect the actual outcome of the Quality Risk Assessment.	
6.1		It would be better to specify that "the other authorized site" could be a warehouse authorized for distribution, according to	

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		GDPs.	
6.3.		After the following sentence: 'Notification by a QP to the releasing site that certification has taken place should be formal and unambiguous and should be subject to the requirements of Chapter 4 of the EU GMP Guide.', the following words should be added: 'and are to be confirmed upfront in a Technical or Quality Agreement.'	
7. Glossary		The definition of 'Batch release' should be added to the Glossary	
Annex		It is proposed to add a model for a Certificate of Compliance of a finished product, to make the request of EEA countries uniform.	

Please add more rows if needed.