2013.10.10

Submission of comments on:

Revision of EU Commission guidelines on GMP for Medicinal Products: Revision of Annex 16: Certification by a Qualified Person and Batch Release

Comments from: Leem (Les Entreprises du Médicament) - France

Name of organisation or individual

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

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Important document which clarifies the responsibilities of Marketing Authorisation holder and Manufacturing and Importation Authorisation Holder. The text consolidates the QP obligations as defined in the different regulatory documentation :European Directives, QP discretion Concept paper ,GMP and GDP. The text insists on the QP responsibilities equivalence between certification and importation activities. Nevertheless, some additional information are necessary to take in account the investigational medicinal products and to be consistent with GMP annex 13. In Addition a clarification should be done regarding the different certification and release activities and the responsibles to be consistent with GMP annex11 and other national regulation in some European countries.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Section 2.1 (Line 20 to 22)	*The ultimate responsibility for the performance of an authorised medicinal product over its lifetime; its safety, quality and efficacy lies with the marketing authorisation holder (MAH).* Comment: In the case of the investigational medicinal products ,the sponsor is concerned Proposed change : The ultimate responsibility for the performance of an medicinal product over its lifetime; its safety, quality and efficacy lies with the marketing authorisation holder (MAH) or the sponsor.	

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)*
Section 2.2 (Line 23 to27)		*However, the responsibility for ensuring that a particular batch has been manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member State where certification takes place and of the destination country of the medicinal product, lies with the QP certifying that batch as being suitable for release.* Comment: This text is not consistent with the requirements contained in article 51a),b) of directive 2001/83/EC and article 55 of directive 2001/82/EC and in article13.3 of directive 2001/20/EC. Only the compliance with the laws in force in the Member State and in accordance with the requirements of the marketing authorisation is required. It's not the QP responsibility of the MIA Holder to know the laws in force in the destination country. Special quality regulation has to be included in MA. In addition take into account the investigational medicine product Proposed change : However, the responsibility for ensuring that a particular batch has been manufactured in accordance with its destination country marketing authorisation, or with the product	

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		specification file, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member State where certification takes place and of the destination country of the medicinal product as described in the agreement signed with the MAH, lies with the QP certifying that batch as being suitable for release. *This is the final step in the process which effectively*	

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Section 2.3.3 (Lines 35 to 38)		*releases the batch for sale or export. This could be done by the QP as an integral part of certification or it could be done afterwards by another person. In this case, this arrangement should be delegated by the QP in a SOP or contract* Comment: This text can be clarified, it could be understood that another person different from a QP can release the product. It is not consistent with GMP annex 11 section 15" Batch release." and with national regulation in some European countries. In addition the investigational medicinal products are released for clinical use by the sponsor. Proposed change (if any) :no proposition	
Section 2.4.3		Any other relevant legal requirements, e.g. of the destination	

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(Line44to45) Section 3.2		country, are taken into account; Comment: Same comment as on section 2.2. It's the QP Marketing Authorisation Holder responsibility to inform the MIAH QP about the legal requirements of the destination country Proposed change : Any other relevant legal requirements, e.g. of the destination country requested by the MAH in an agreement are taken into account;	

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(Line 53 to 56) Section 3.3		*Any QP involved in the certification, or confirmation, of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to demonstrate knowledge of the product type, production processes, technical advances and changes to GMP .* Comment: Text to be adapted to be applicable Proposed change: Any QP involved in the certification, or confirmation, of a batch must have detailed knowledge of the steps for which they are taking responsibility. The QPs should be able to proof his/her continuous training regarding the product type, production processes, technical advances and changes to GMP	

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Section 3.3		*Manufacturing steps performed at sites in the EEA* Comment: Take into account the specificities of the investigational medicinal products Proposed change : It should be made reference to GMP annex13 for the investigational medicine product	

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(Line 89) Section 3.3 i)		*A template for the confirmation is presented as an Attachment.* Comment: The companies should be able to adapt the template if necessary Proposed change : A template example for the confirmation is presented as an Attachment	

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Lines 82 to 83)		*"in a written agreement between the sites where the QPs are <u>located</u> at different manufacturing authorisation holders. «* Comment: Under the legal view, the engagement of the QP at a legal entity is relevant and not the location only Proposed change : "in a written agreement between the sites where the QPs are <u>located and committed</u> at different manufacturing authorisation holders."	

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Section 3.4.2 (lines 97 to100)		*Importation activities including at least receiving, sampling, storage of the un-released and un-certified batch, quality control testing, certification and release should be conducted by authorised sites in the EEA according to the requirements of Directive 2001/83/EC, Directive 2001/82/EC and Directive 2001/20/EC.* Comment: It should be under the Importer authorisation Holder responsibility to identify the sampling location based on an risk analysis according to GMP annex 20 Proposed change (if any) :no proposition	

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Section 3.4.5 (Lines 110 to 115)		*Also, unless an MRA or similar agreement is in place between the EEA and the exporting country, that it has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary, or in accordance with an approved Real Time Release Testing programme to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation* Comment: Take into account the specificities of the investigational medicine products Proposed change : It should be make reference to GMP annex 13 for the investigational medicine product	

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Section 3.4.6 (Lines 116 to117)		*Sampling of imported product should in full be representative of the batch and, therefore, be taken after arrival in the EEA* Comment: The different concerned samplings should be clarified: for testing, for reference and for retention samples according to GMP chapter 6 and annex 19. It should be taken in account the possibility to validate the transport to avoid waiting for the arrival of the batches in EEA to do the sampling of the product, see also the comments in section 3.4.2 Proposed change : Sampling for testing,reference sample and retention sample of imported product should ~~in full~~ be representative of the batch according to the requirements of GMP chapter 6 and GMP annex 19	

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Section 3.4.8 (lines 124 to 128)		*When different finished product batches originating from the same bulk product batch are imported, the QPs certifying the different finished product batches may base their decision on the quality control testing of another imported finished batch originating from the same bulk product batch <u>provided that the ID and assay testing are conducted on each occasion</u> within the EEA and there is secured documented evidence that..* Comment: Testings in this case have to be defined if needed by the QP according to a risk analysis Proposed change : When different finished product batches originating from the same bulk product batch are imported, the QPs certifying the different finished product batches may base their decision on the quality control testing of another imported finished batch originating from the same bulk product batch <u>based on an risk analysis</u> and there is secured documented evidence that..	

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Section 3.5		*Operational responsibilities of the QP prior to certification of a batch for release to market or for export, the QP must <u>personally</u> ensure that…* Comment: Introductory sentence doesn't make sense .Suggest should be similar format as sections 3.3, 3.4, 3.7 and 3.8. The word "personally" has a strong impact , it's not realistic and not consistent with the possibility to delegate some activities as defined in section 3.5.3 Proposed change : 3.5 Operationnal responsibilities of the QP "Prior to certification of a batch for release to market or for export the QP must ~~personally~~ ensure that.."	

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Section 3.5.9 (Lines 159 to 162)		*The active substances used in the manufacturing of the finished products have been manufactured in accordance with GMP and, where required, imported and distributed in accordance with Good Distribution Practices (GDP). When imported, and as relevant,the requirements of Article 46b of Directive 2001/83/EC are met.* Comment: Incorrect reference Proposed change : *"..When imported, and as relevant, the requirements of Article 46 ter b) of Directive 2011/62/EC are met.*	

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Section 3.8.2 (Lines 211to 214)		*The control report referred to in Article 51 of Directive 2001/83/EC or Article 55 of Directive 2001/82/EC or another proof of certification for release to the market in question based on an equivalent system should be made available for the batch in order for the batch to be exempted from the controls when entering another Member State.* Comment: It could be taken into account the manufacturing entities belonging to the same group with the same quality system for which control report or certification proof are not necessary. Proposed change :no proposition	

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Section 4.2.4 (Lines 433 to 434)		*The QP should ensure that a written final assessment and approval of third party audit reports has been made by the company according to the company´s requirements.* Comment: This section has to be changed to consider each Company organisation and quality system Proposed change : The QP should ensure that a written final assessment and approval of third party audit reports has been made as defined by the company's quality system and according to the company´s requirements.	

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Section 5.2 (Lines 247 to 249)		*Where a deviation has occurred during manufacture or testing of a batch of finished product it may be considered to meet the requirements of the marketing authorisation and GMP when the details described below have been taken into account….* Comment: Deviation occur not only during manufacture or testing. Storage and transport can be included according to the requirements in section 3.4.4. Proposed change : Where a deviation has occurred during manufacture, testing, storage or transport of a batch of finished product, it may be considered to meet the requirements of the marketing authorization and GMP when the details described below have been taken into account…. ***Content of the confirmation of the partial manufacturing of a***	

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Template of confirmation letter Title		***medicinal product /investigational medicinal product*** Comment: To clarify when to use this confirmation letter only when the QPs are operating under different manufacturing authorisation holder and when a written agreement is necessary according to the section 3.3 i) Proposed change : **Content of the confirmation of the partial manufacturing of a medicinal product /investigational medicinal product <u>for QPs operating under different manufacturing authorisation holders</u>**	

Please add more rows if needed.