<04/04/2013>

Submission of comments on 'Guidelines on the formalised risk assessment for ascertaining the appropriate good manufacturing practice for excipients of medicinal products for human use'

Comments from: Leem (Les entreprises du Médicament)

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.

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)***
	The overall concept is relevant but until the requirement for registration of the Excipient Manufacturer is in place and the disclosure by the suppliers of the Manufacturer's name (e.g., on the Certificate of Analysis) is made mandatory, the actual risk analysis described in the document (section 2) and the confirmation of the application of appropriate GMP (§ 17e) will not be possible as such.	
	It should be considered that, in many cases, excipient are manufactured according to quality systems which refers to the food regulation (e.g. ISO-22000) and that manufacturers are not aware such material is used as Pharmaceutical Excipient. In such case, risk analysis must lead to an acceptable conclusion of the quality system, based on experience and impact of excipient's quality on the medicinal product safety and efficiency	

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)***
§ 5		Comment: Manufacturers of medicinal product must have a risk assessment/management documentation… not importers of the medicinal product Proposed change (if any): Manufacturers of medicinal products, as well as manufacturers of semi-finished products must have the risk assessment /management documentation of the excipient manufacturer and supplier , for appropriate GMP for excipients available on site	
§8		Proposed change (if any): Bullet point to be added: ▪ Packaging integrity evidence ▪ Cold chain management, if appropriate	
§8 bullet point 6 & 7		Proposed change (if any): ▪ Use of dedicated equipment and/or facilities at the excipient manufacturing site, when needed ▪ Environmental control & storage conditions at the excipient manufacturing site, if needed	

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)***
§9		Comment: For this guidance, The different items have to be considered as examples. Proposed change (if any): Additionally, the Manufacturing Authorisation Holder could also consider during its assessment ~~with respect to~~ the use and function of the ~~each~~ excipient ~~the Manufacturing Authorisation Holder should also consider~~ such as:	
§ 9 bullet 4		Proposed change (if any): "Daily patient intake of the medicinal product containing the excipient"	
§ 9 bullet 7		Comment: The sentence is not clear enough Proposed change (if any): "Potential impact of the excipient on the Critical Quality Attributes of the medicinal product"	

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)***
§ 11		Proposed change (if any): This will vary depending on the source, the supply chain and the subsequent use of the excipient, but as a minimum the following high level GMP principles should be considered by the excipient manufacturer (exceptions to be justified) :"	
Section 3			

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)*
§ 15		Comment: The documentation should be made as a result of the gap analysis: this part was added above in section 12. The requirement of the Directive 2011/62/EU is to determine the GMP applicable to the excipient based on a risk assessment. Therefore the risk profile of the excipient manufacturer is out of scope of this document.	
§ 16		Comment: "Acceptance" and "Unacceptable" are not mitigation strategies, these are conclusions Proposed change (if any): "From the gap analysis result, The Manufacturing Authorisation Holder must determine the status of the excipient as acceptable, requesting control or unacceptable. A control strategy (e.g. audit, document retrieval and testing) should be established whenever an excipient continues to be used while under "requesting control"status.	

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)***
§ 17 item e		Comment: all other items are related to a outcome, this should be aligned for item e It must be underlined that audit of excipient manufacturer is nor a regulatory requirement, and quality system may be assessed through documentation review Proposed change (if any): "Outcome of the quality assessment ~~Audit (re-audit)~~ of excipient manufacturer"	
Missing		Comment: The risk review must result in an adjustment of the control strategy if required Proposed change (if any): add the sentence as section 18 "Based on the outcome of the risk review, the established control strategy should be reviewed and revised if needed"	

Please add more rows if needed.