EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<26 April 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' (SANCO/D/6/SF/mg/ddg1.d.6(2013)179263)

Comments from:

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1. General comments

Stakeholder number (	General comment (if any)	Outcome (if applicable)
	EFPIA welcomes the opportunity to provide comments on this guideline. In general we support the development of risk based guidance to help determine the appropriate level of GMP for the manufacture of excipients, define the responsibilities of the manufacturer and how these responsibilities can be fulfilled through reliance on effective site or global quality systems; and are appreciative of the approach, structure and level of detail the guideline provides. Pharmaceutical manufacturers are responsible for ensuring that excipients used in medicinal products are fit for purpose. This principle is already embedded in EU GMP for medicinal products for human use (e.g. EU GMP Chapter 5). In accordance with the current requirements of EU GMP, the pharmaceutical industry has vendor management systems in place. In these programmes, the quality systems at the excipient supplier and the corresponding Good Distribution Practices associated with the excipient in the supply chain are monitored and audited. Risk assessments are routinely performed taking into account the type of excipient, the quality history of the excipient supplier and the reliability and integrity of the supply chain. The use of the excipient in the finished product and its route of administration is also considered in the risk assessment. We see this guideline as complimentary and supportive of existing GMPs and expectation.	
	The guideline could benefit from further clarity regarding it's' scope as it is currently unclear whether this guideline applies to commercial products only, or if it also applies to Investigational Medicinal Products.	
	The guidance requires the Manufacturing Authorisation Holder to determine and	

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	document an appropriate level of GMP based on a risk assessment there could be differences between implementation as to the acceptability of a company's approach. In due course it may be helpful to provide examples or guidance through dialogue with industry, we would recommend that the EMA consider developing a list of questions and answers to support the implementation of the guidance and provide a level of clarity and expectation. Some examples of potential questions are listed below. **Suggested questions for Q&A:** 1. Do I need to perform risk assessments for all established products in addition to new product introductions or changes of excipient/supplier? (relates to Section 2) 2. Do I have to perform an excipient risk assessment for my investigational medicinal product? (Section 2) 3. What sources of excipients are considered high risk? (Paragraphs 8 & 11) 4. What factors should be considered as delivering a high risk excipient? (Paragraphs 7 & 8) 5. What does full traceability mean? (Paragraph 11h) 6. What uses for an excipient would be considered high risk? (Paragraph 9) 7. How does the amount of excipient used affect the risk rating? 8. How does the manufacturer defect history impact the risk assessment in relation to the appropriate GMPs required? (Paragraph 17) 9. My excipient manufacturer has the appropriate level of GMP however the process of manufacture/extraction can lead to some variability and defect.	

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	Increasing GMP requirements on the manufacturer will not increase the reliability. What should I do? (Paragraph 17) 10. I have an excipient that is common across a range of products and is sourced from a single supplier, is there a need to do a product by product risk assessment? (Paragraph 9) 11. We have multiple excipients from one supplier is there a need to perform individual risk assessments for this supplier? (Section 3 & Paragraph 17)	

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)*
Paragraph 1		**Comment:** Correct reference to directive (2011/83/EC is incorrect). **Proposed change (if any):** Change to 2001/83/EC.	
Paragraph 5		**Comment:** Manufacturers of medicinal product must have a risk assessment / management documentation available, not the importers of the medicinal product. **Proposed change (if any):** Change 'importers' to 'manufacturers'.	
Paragraph 7		**Comment:** Section #7 is too prescriptive. An appropriate risk scheme should be in place but this guideline should not define the specific ranking. **Proposed change:** Remove reference to "low risk", "medium risk" or "high risk".	
Paragraph 8		**Proposed change (if any):** Additional items to be added as bullet points: • Packaging integrity evidence • Cold chain management, if appropriate	
Paragraph 9 (bullet 3)		**Comment:** The quantity used of the excipients for the manufacture of the medicinal product is not providing a strong indication. **Proposed change (if any):**	

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		"The proportion of the excipient in the medicinal product composition."	
Paragraph 9 (bullet 6)		**Comment:** Reword for better clarity. **Proposed change (if any):** "The nature of the excipients (i.e., pure or composite)."	
Paragraph 10:		**Comment:** EFPIA believes that it is not necessary to develop additional GMP guidelines for excipients. For instance, reference could be made to, inter alia, IPEC/PQG Excipient Guide 2006 (based on ISO framework). Also, EU-GMPs are established for finished drug products and APIs and not for excipients. therefore it is suggested to remove references from section #10. **Proposed change (if any):** Having established and documented the risk profile of the excipient, the Manufacturing Authorisation Holder should establish and document the elements of GMP that he believes are needed to be in place in order to control and maintain the quality of the excipient	
Paragraph 11 (point c)		**Comment:** EU GMPs refer to job descriptions for staff in responsible position, and do not use the term "managerial and supervisory staff". **Proposed change (if any):** "Defined job descriptions for staff in responsible positions … ."	
Paragraph 11 (point g)		**Comment:** Align with common practice to use a retest period, rather than	

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		an expiry period. **Proposed change (if any):** "… which should be for at least one year after the expiry date or retest period of the excipient batch to which it relates."	
Paragraph 16		**Comment 1:** Risk acceptance is not a mitigation strategy, it is 'conclusion'. **Comment 2:** The meaning of 'document retrieval' is not clear. We suggest to replace it by 'documentation based'. **Proposed change (if any):** "The Manufacturing Authorisation Holder must determine the status of the excipient as acceptable , requesting control or unacceptable. Control strategies (e.g. audit, documentation based, and testing) appropriate to the different risk profiles should be established."	
Paragraph 17		**Comment:** Clarify that "risk profile of the manufacturer" means the "excipient manufacturer". **Proposed change (if any):** "Once the 'appropriate GMP' for the excipient and the risk profile of the excipient manufacturer has been defined on-going risk review should be performed through mechanisms such as: …"	
Paragraph 17		**Comment:** Add other relevant items (as additional sub-points). **Proposed change (if any):** Add: observed organizational, procedural or technical/process	

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		changes at the excipient manufacturer".	

Please add more rows if needed.