18 July 2013

GMP revision: Chapter 5 - Production

Comments from:

Name of organisation or individual
AESGP

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)*
	We refer to our comments on the 'EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (annexed to this document) and again ask that both the PDE approach and the current approach be equally acceptable. Companies should be left the choice of the approach they want to follow.	

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)*
Chapter 5 (Production) 5.19		Comment: With reference to our comments on the 'EMA Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' (annexed to the present document), applying the PDE approach to all APIs and finished products would be excessive and would be extremely cost and resources-demanding for companies (particularly those with a large portfolio of older/ well-established products or products with a small market share- those two kinds are very common in the self-care sector) whilst generating minimum value added. We believe that the performance of toxicological evaluation should be left to the decision of the company. Both the PDE approach and the 'current approach' should be equally acceptable. The PDE-approach may particularly benefit hazardous contaminants such as highly sensitizing materials (such as beta lactams), biological preparations (e.g. from live micro-organisms), certain hormones, cytotoxics and other highly active materials. (see also Chapter 3, no. 3.6) Proposed change (in bold): A Quality Risk Management approach should be used based upon the potential cross contamination risks presented by the products manufactured. Factors including: facility/equipment design, personnel flow, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative **to acceptance criteria (e.g. 10 ppm, 1/1000**	

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		dosis) should also be taken into account. … or product family. This may range from … entire manufacturing facility. It may be acceptable … , where justified. The outcome of the Quality Risk Management process should be the basis for determining the necessity for and extent to which equipment and facilities should be dedicated to a particular product or product family. This may range from dedicating specific product contact parts to dedication of the entire manufacturing facility. It may be acceptable to confine manufacturing activities to a segregated, self contained production area within a multiproduct facility, where justified. **In case the PDE approach is chosen by the company for example for specific products, such as highly sensitising materials (e.g. penicillins), biological preparations (e.g. from live micro-organisms), certain antibiotics, certain hormones, certain cytotoxics or certain highly active drugs,** a toxicological evaluation should be the basis for the establishment of threshold values in relation to the products manufactured (see Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities). Where the toxicological evaluation supports a threshold value, this should be used as an input parameter in risk assessment.	
5.27, 3rd paragraph		Comment: The medicinal product manufacturer has commonly no contacts or	

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		business agreements with the active substance starting materials manufacturers. It is however the responsibility of the medicinal product manufacturer to check during the audit of the active substance manufacturer that the active substance manufacturer has supply chain and traceability records of the active substance starting materials. Proposed change: The supply chain and traceability records for each active substance ~~(including active substance starting materials)~~ should be available and be retained by the EEA based manufacturer or importer of the medicinal product.	
5.27; 4th paragraph		Comment: In exceptional circumstances where direct audit of the active substance manufacturer is not possible, other arrangements for verifying the GMP status of the active substance manufacturer may be deemed acceptable. This could include for exemple remote audit (cf EMA GMP Q&A 3 under GMP PaRT II) and cover the very specific situation of atypical actives. Proposed change (in bold): Audits should be carried out at the manufacturers and distributors of active substances to confirm that they comply with the relevant good manufacturing practice and good distribution practice requirements. The holder of the manufacturing authorization shall verify such compliance either by himself or through an entity acting on his behalf under a contract. **In exceptional circumstances, other evidence may be provided in lieu of audit (e.g. remote audit or other situations applicable to non-traditional /**	

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		atypical active substances). For veterinary medicinal products, audits should be conducted based on risk.	
5.33, lit b)		Comment: Both active substances and excipients belong to starting materials. Whereas the qualification of an active substance manufacturer is based on an audit, excipients manufacturers can also be qualified by other tools/activities. Proposed changes (in bold): b) The finished product manufacturer should perform **a verification, which might include** audits at appropriate intervals at the site(s)**,** carrying out the testing (including sampling) of the starting materials in order to assure compliance with Good Manufacturing Practice and with the specifications and testing methods described in the Marketing Authorisation dossier.	
5.68		Comment: We acknowledge that the issue of shortages is an important one and that in some cases it could be due to manufacturing issues. However, we do not find it appropriate to reflect here potential consequences of productions issue as this is not really the purpose of a GMP guideline. In addition, the topic of shortages is a very complex one which would merit being addressed separately with all different facets (manufacturing, economical, trade, etc.) being dully reflected. Adding it here also gives the false impression that only GMP/production issues are the cause of shortages. Proposed changes: please delete the paragraph	

Please add more rows if needed.

AESGP comments on GL on setting health b