<2013-06-24>

Submission of comments on:
Revised Chapter 3 of European GMP guide on Premises and Equipment
Revised Chapter 5 of European GMP guide on Production

Comments from:

Name of organisation or individual
EFPIA

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)*
	The opportunity to apply science- and risk-based approaches to the avoidance of cross-contamination is welcomed. Nevertheless, it is extremely important that the revisions to Chapters 3 and 5 concerning the avoidance of cross-contamination are carefully considered in relation to the proposed 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities', such that the scope of toxicological evaluations is focused on the products of greatest concern, and that the requirements do not result in significant changes to current industry practices that could adversely impact the availability of medicines.	
	The major areas of concern are highlighted in more detail in the efpia response to the 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' which includes commentary on the application of toxicological evaluations to Investigational Medicinal Products and late stage development products, and existing products.	
	Industry understands that there is a firm commitment from the EMA to conduct a practical workshop between agency and industry to work through the 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal	

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	products in shared facilities'. In view of the complexity of this topic, such a workshop is strongly advocated by industry, timed to take place before the guidance and chapter 3 and 5 revisions are finalised. In particular section 5.19 should be revised based on the outcomes of the workshop.	
	Section 5.33 of the proposed revision to Chapter 5 is also recommended for revision to improve the clarity of the requirements. As currently written the text appears to mix general requirements for testing of starting materials with specific requirements relating to the outsourcing of such testing.	

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 3		**Premises and Equipment**	
3.6		Comment: The reference to the Guideline is cited twice in this paragraph – the later reference is more appropriate. Proposed change (if any): ~~(see Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities).~~	
3.6		Comment: The description here implies that a toxicological evaluation is needed for all products. It would be a significant undertaking to have a formal evaluation in accordance with the requirements as written in the draft 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities' for all existing products, and, for products with known low toxicity potential, of little value for protection of patients. Proposed change (if any): The scope, in terms of products needing the toxicological evaluation, should be defined so that the effort usefully contributes to the protection of patients. We propose that the toxicological evaluation effort is focused on appropriate products (e.g. certain high potency anticancer drugs or DNA reactive compounds, certain hormones and extreme sensitisers), for example by using QRM to assess general risks	

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		and classes of products being manufactured. (This is further detailed in the Efpia comments on the draft 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'.)	
3.23		Comment: Physical segregation for the storage of rejected, recalled or returned materials or products is implied. Electronic segregation using a validated Warehouse Management System should be permissible. Proposed change (if any): Segregated areas, or other means of segregation, should be provided for the storage of rejected, recalled or returned materials or products.	
Chapter 5		**Production**	
5.15 and elsewhere		Comment: The term Quality Control Department seems to be used where in fact it should be Quality Assurance Department. Proposed change (if any): Consider changing to 'Quality Department'	
5.17		Comment: A clarification regarding the definition of non-medicinal and medicinal products is needed. Example: • Ectoparaciticides may be registered as non-medicinal whereas Endoparaciticies may be registered as medicinal. • Certain ectoparasiticides manufactured in Europe are licensed as veterinary medicinal products and are governed by EU Directive 2001/82/EEC as amended.	

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		They are not considered as pesticides based on registration and do not fit into the definition of 'technical poisons' as specified in EudraLex Volume 4, chapter 3, 3.6. Consequently these products can be manufactured in premises used for the manufacture of medicinal products. Proposed change (if any): The production of technical poisons, such as certain pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.	
5.18		Comment: Clarification of text used in this section is required. The additions to text in the section "This risk of accidental cross-contamination arises from ..." have resulted in a confusion about the factors to which the uncontrolled release apply. This would be clearer if a bulleted list, for example. Proposed change (if any): This risk of accidental cross-contamination arises from uncontrolled release of materials (including dust, gases, vapours, sprays, genetic material or organisms) arising from • active substances • other starting materials • in-process materials and/or from residues on equipment or operators' clothing.	
5.18		Comment: "…by robust design of the premises, equipment and processes" – unclear what is 'robust' design. Proposed change (if any): "… by appropriate design of the premises, equipment and	

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		processes.”	
5.18		Comment: It would be helpful if the distinction between "dedicated facilities" and "dedicated equipment” could be made. Certain products could be manufactured within shared facilities, providing the equipment for such products is dedicated and measures to mitigate the risks of cross-contamination are applied. Examples might include liquid manufacturing, or production within completely closed pieces of equipment. This seems to be acknowledged in the technical and organisational measures listed in 5.20. Proposed change (if any): Consider making this more explicit here and/or in section 5.20.	
5.19		Comment: The description here implies that a toxicological evaluation is needed for all products. It would be a significant undertaking to have a formal evaluation in accordance with the requirements as written in the draft ‘Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities’ for all existing products, and, for products with known low toxicity potential, of little value for protection of patients. Proposed change (if any): The scope, in terms of products needing the toxicological evaluation, should be defined so that the effort usefully contributes to the protection of patients. We propose that the	

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		toxicological evaluation effort is focused on high toxicity products, for example by using QRM to assess general risks and classes of products being manufactured. (This is further detailed in the Efpia comments on the draft 'Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities'.)	
5.20		Comment: There is an opportunity to update terminology in line with ICH Q9 - 'risk control measures' Proposed change (if any): Technical and organisational measures to mitigate and control risks of cross-contamination …	
5.21		Comment: There is an opportunity to update terminology in line with ICH Q9 - 'risk review' Proposed change (if any): Measures to prevent cross-contamination and their effectiveness should be reviewed according to set procedures.	
5.26		Comment: References to Marketing Authorisation dossiers imply that Section 5.26 – 5.36 are not applicable to IMPs. It would be helpful to clarify this in the document. Proposed change (if any): Clarify the applicability to IMPs at the beginning of section 5.26.	
5.27		Comment: Requirements relating to active substance starting materials	

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		are defined in EU GMP Part II and in some points go beyond what is suggested in this part. The traceability requirements specified in 5.27 may be problematic because the source of active substance starting material is described in the closed part of the dossier (EDMF, CEP). Proposed change (if any): Supply chain traceability should be established and the associated risks, from active substance to the finished medicinal product, should be formally assessed and periodically verified. Appropriate measures should be put in place to reduce risks to the quality of the active substance. The supply chain and traceability records for each active substance should be available and be retained by the EEA based manufacturer of the medicinal product or importer of the active substance.	
5.27		Comment: Manufacturing Authorisation Holders are responsible for ascertaining the appropriate GMP for excipients and ensuring that it is applied. Proposed change (if any): <u>Excipients</u> Manufacturing Authorisation Holders are responsible for ascertaining the appropriate GMP for excipients, on the basis of a formalised risk assessment, and ensuring that it is applied.	
5.33		Comment: Elements included in this section are described in other parts of EU GMPs. It may be simpler to provide a high level	

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		summary of the key areas for consideration and reference the relevant section. Proposed change (if any): The rationale for the outsourcing of this testing should be justified and documented. The requirements are described in other parts of the EU-GMPs: a) Outsourced activities (Chapter 7) *<delete text under a>* b) Self inspections (Chapter 9) *<delete text under b>* c) Quality Control (Chapter 6) *<delete text under c>* d) Change Control (see in Chapter 1) *<delete text under d>*	
5.68		Comment: Consider avoiding repeating text from legislation in the EU-GMP. As a general principle it may be helpful to avoid including detail from other parts of the EU GMP and/or Directives as any changes will then require revisions of multiple documents. (Note also there is only one set of quotation marks at the beginning of the text) Proposed change (if any): Suggest replacing the text by - The holder of a marketing authorisation for a medicinal product should, within the limits of their responsibilities, ensure appropriate and continued supplies of the medicinal product and should notify the competent authority if the product ceases to be placed on the market of the Member State, either temporarily or permanently. (see Article 81 of Directive 2001/83/EC, Article 23a of Directive 2001/83/EC and amendments, if applicable)	

Please add more rows if needed.