<18 July 2013>

Submission of comments on EudraLex,
The Rules Governing Medicinal Products in the European Union, Volume 4

EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, Part 1. Chapter 5: Production

document title>' (EMA/…/…)

Comments from: APIC

Name of organisation or individual
APIC

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)*
	APIC supports the Revision of Chapter 5 of the EU Guidelines for good manufacturing practices to give improved guidance on prevention of cross contamination with reference to the complementary toxicological assessment guidance. The use of Quality Risk Management Principles and the evaluations of the Health Risks towards patients should support Companies and Regulators to decide when Dedicated Facilities or units of facilities are needed for Higher Risk categories of Active Substances and Medicinal Products.	
	APIC also supports the changes to sections 26 to 28 on the qualification of suppliers and to the other changes introduced.	

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 5.17		Comment: Please clarify the scope of non-medicinal product. For example could OTC products be manufactured in equipment used for Medicinal Products? Please clarify if storage as well as the production of technical poisons is not allowed together with medicinal products.	
		Proposed change (if any): Normally, the production of non-medicinal products should be avoided in areas and with equipment destined for the production of medicinal products but in exceptional circumstances could be allowed where the measures to prevent cross contamination with medicinal products described below and in Chapter 3 can be applied. The production and storage of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.	
Section 5.18		Comments : 1) In this section, the concept of risk analysis should be further emphasised. See proposed text below. 2) Risk assessment concepts appear in 5.19. Please consider to merge sections 5.18 and 5.19. 3) Please consider including packaging materials and personal flows in the text. 4) Please clarify that cleaning validation should be targeted towards those parts of the premises,	

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		equipment and facility that pose a significant risk for cross contamination. In Active Substance Facilities for example, the equipment used for early production steps that, after cleaning, is used for subsequent production steps in sequence may not pose a significant risk of cross contamination and so cleaning validation may not be necessary. Proposed Change:- Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapours, sprays, genetic material or organisms from active substances, other starting materials, products in process, from residues on equipment, from packaging materials, from personal flow and operators' clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Products in which cross contamination is likely to be most significant are those administered by injection and those given over a long time. Cross contamination should be avoided by robust design of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by appropriate risk assessments, procedures and technical or organizational measures, including reproducible cleaning and decontamination processes of validated effectiveness.	
Section 5.19		Comment: Please include microbiological controls as one of the Risk Factors and allow for self-contained production area within multi-product facilities within the wording of this section.	

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		Proposed Change: 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. A Quality Risk Management approach should be used based upon this toxicological evaluation and the potential cross contamination risks presented by the products manufactured. Factors including; facility/equipment design, personnel flow, microbiological controls, physico-chemical characteristics of the active substance, process characteristics, cleaning processes and analytical capabilities relative to the threshold values for products should also be taken into account. 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.	
Section 5.20		Comment: Organisational Measures. Bullet Point 3 states the following:- • Cleaning verification after each product campaign	

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		instead of a cleaning validation should be considered as a detectability tool to support effectiveness of the Quality Risk Management approach. Please clarify if this means that a cleaning verification would be an acceptable or even a preferred alternative to cleaning validation in certain cases.	
Section 5.20		Comments: 1) Please include personal and equipment flows in Technical Measures, bullet point 3. 2) Please include associated tools in Organisational Measures bullet point 2. Proposed Changes:- <u>Technical Measures</u> • design of manufacturing process, facility, equipment and flows (personal, equipment, …) to minimise opportunities for cross contamination during processing, maintenance and cleaning. <u>Organisational Measures</u> • Dedicating the whole manufacturing facility or a self-contained production area on a campaign basis • (dedicated by separation in time) followed by a cleaning process of validated effectiveness, • Keeping protective clothing and associated tools inside areas where products with high risk of cross-contamination are processed,	
Section 5.26		Comment: The following sentence is too restrictive. "Where possible starting materials should be purchased directly from the manufacturer of the starting material". The minimum requirement should be that the original	

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		manufacturer is known.	
		Proposed change:- Where possible starting materials should be purchased directly from the manufacturer of the starting material. Where starting materials are purchased from suppliers, the name and address of the original manufacturer should be known.	
Section 5.26 and 5.33 a)		Comment: Clause 5.26 states:- "The quality requirements established by the manufacturer for the starting materials should be discussed and agreed with the suppliers. Appropriate aspects of the production, and control, including handling, labelling, packaging and distribution requirements, complaints, recalls and rejection procedures should be documented in a quality agreement or specification". Proposed change (if any): The formal agreement between the finished product manufacturer and the starting material manufacturer is also covered in clause 5. 33. We propose that you re-group these clauses together.	
Section 5.33 b)		Comment: Please clarify that responsibility for auditing contract laboratories may be delegated by the medicinal product manufacturer to the active substance manufacturer / supplier. In this case, responsibilities should be defined in Quality Agreements between Medicinal Product manufacturer, sub-contracted laboratory and active substance manufacturer / supplier. Proposed change: Add the following text at the end of 5.33 b):	

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		Responsibility for auditing contract laboratories may be delegated by the medicinal product manufacturer to the active substance manufacturer / supplier. Responsibilities should be defined in Quality Agreements between the medicinal product manufacturer, sub-contracted laboratory and active substance supplier.	
5,33 c)		Comment: Clause 5.33 c) states: "The certificate of analysis provided by the starting material manufacturer should be signed by a designated person with appropriate qualifications and experience. This person should ensure that each batch has been manufactured and checked for compliance with the requirements of the formal agreement". It is quite hard for the designated person to ensure this. Moreover, this would require a customization of each CoA for each customer. Please clarify what is intended in this case.	
Section 5.33 d)		Comment: Please give guidance on what is meant by and how to assess significant experience in the following sentence:- The finished product manufacturer should have a significant experience in dealing with the starting material manufacturer including assessment of batches previously received and the history of compliance before reducing in-house testing.	
General		Comment: As a general comment, it would be better to be more logical on the structure of Chapter 5. In the proposed draft, topics of starting material, API, excipient and packaging are mixed. Please consider to re-	

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		group information on the same theme. For example: Starting Material API Excipient Packaging	

Please add more rows if needed.