ISPE Regulatory Comment Form

Proposed Regulation/Guidance Document: European Commission 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

Comments submitted by: ISPE | 600 N. Westshore Blvd., Suite 900 | Tampa, FL 33609 | +1-813-960-2105 | www.ispe.org

General Comments
It is important to understand the scope of this change particularly in relation to the implementation date. For new factories/plants or new products the new requirements would be implemented in the design/development process. For established products and plants it could require a major piece of work to perform risk assessments and evaluations which could result in minor or extensive actions.

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	5.17	Include hazardous laboratory chemicals.	Amend 5.17 second sentence to: "The production of hazardous laboratory chemicals and technical poisons, such as pesticides and herbicides, should ...."

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	5.18	It is not clear what is meant by decontamination in addition to cleaning in the second paragraph of this section. Decontamination could be used in several contexts - decontamination of product contact surfaces, decontamination of non-product contact surfaces like surfaces in rooms and operators clothing, decontamination (microbiological) of surfaces by for example hydrogen peroxide for sterile products. Would validation be expected for decontamination of non-product contact surfaces including establishing limits and methods for sampling and analyses? The first line of the new paragraph on avoiding cross contamination by 'robust design' is vague. Based on other proposed changes, one might expect the 'robust design' to be based on the outcome of an appropriate risk assessment process.	Clarify the difference: decontamination vs cleaning. Clarify if cleaning/decontamination validation applies to only product contact parts or both product contact parts and non-product contact parts. Amend the first line of the second paragraph to: "Cross contamination should be avoided by use of an appropriate risk assessment processes to give a robust design of the premises, equipment...."
	5.19	The significance of material flow is not reflected in the statement	Amend the fourth sentence to read:. "Factors including; facility/equipment design, personnel flow, material flow, physico-chemical characteristics of the active substance...."

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	5.20 Technical Measures 2nd bullet	Material introduction and waste disposal should be separated	Amend the 2nd bullet to read: • Self-contained production areas having separate processing equipment, material introduction, waste disposal and separate HVAC systems. It may also be desirable to isolate certain utilities from those used in other areas.
	5.20 Technical Measures 8th bullet	Importance of elimination of any risk of cross-contamination is recommended.	Amend the 8th bullet to read: "use of single-use disposable technologies".
	5.20 Organizational Measures 3rd bullet	For non-english speakers the difference between the two terms, i.e. validation and verification may not be readily apparent.	The difference in meaning of the terms validation and verification should be detailed and/or both terms referenced in the GMP glossary.
	5.20 Organizational Measures 3rd and 4th bullets	The texts for these two bullet points describe basically the same process i.e. cleaning verification. This term is only used in the case of product campaign. Is this intentional? Is the 'comprehensive sampling protocol for critical surfaces anything basically different from a 'detectability tool' for the cleaning effectiveness?	The texts for these two bullet points should be made clearer/unambiguous if a difference in scope and/or depth is intended; otherwise the texts should be united.

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	5.20 Organizational measures 4th & 5th bullet	The mechanisms and routes of cross contamination are not clearly identified, which makes establishing whether particular controls are appropriate in a particular case difficult. Generic cross contamination routes should be identified in the guideline. We recognize the fact that surface and air samples have to be taken in some cases (to determine operator exposure). The use of such samples to demonstrate risks for contamination of products will be difficult since there is no correlation between a certain level of contamination on a surface/in an air volume and the product. As such it would be difficult to set acceptance limits or interpret results for this type of indirect contact (other than use it as an indication of a proper design).	Amend bullets 4 & 5 to to identify generic cross contamination roots. Amend bullets 4 & 5 to indicate that if a correlation exists or is suspected between the level of contamination and on a surface/in an air volume and the product then acceptance limits can be set for this form of indirect contact.

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