Connecting a World of Pharmaceutical Knowledge

17 July 2013

EUROPEAN COMMISSION
Health and Consumers Directorate-General

Subject: **Revision of EU Commission guidelines on Good Manufacturing Practice Medicinal Products**

Dear Sir or Madam,

Thank you for the opportunity to comment on the above draft guidelines.

ISPE supports the changes to Chapters 3, 5, 6, and 8 of the European GMP Guide and welcomes clarification of steps that can be taken to prevent aspects of cross contamination.

As changes to Chapters 3 and 5 are similar, not surprisingly some of our general comments are also similar. In this respect, ISPE members have a particular concern as to the impact of the speed of implementation of the changes and the potential impact on the industry and product supply.

These changes have the potential to impact other regulatory documentation. There is, however, no mention of any such potential associated regulatory changes either in the cover note or in the text. As such, it is not clear if this is simply an oversight or if, in fact, no such change is envisaged.

ISPE is pleased to make both general and specific comments to the guideline as detailed in the attachments to this letter. In the apparent absence of a standard EC comment form we have utilised a generic template and trust this is acceptable.

The International Society for Pharmaceutical Engineering (ISPE) is an individual membership Society of more than 20,000 professionals involved in the manufacture of pharmaceuticals and related products. All scientific and technical areas of the pharmaceutical manufacturing industry are represented among the ISPE Membership. ISPE is committed to creating a forum for uniting the world's pharmaceutical manufacturing community and regulators.

Yours sincerely,

President/CEO, ISPE

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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 3: Premises and Equipment***

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

General Comments
The cover sheet to this GMP change details an implementation date of 6 months. The expectation on implementation of the new requirements for existing products/processes/facilities is no, however, clear. Depending on several factors as to when products were developed, available toxicological data, existing validation data and design of equipment and facilities, the consequences of this GMP change could be minor or quite extensive. If the new requirements are expected to be implemented for all existing products and facilities there would be a need for a longer implementation timeframe (after the new regulations have come into operation) in order to allow for new risk assessments to be performed and, if needed, new validations and changes to equipment and facilities.
The timetable for the proposed date for the new draft Annex 15 is December 2013, i.e. potentially after or at a similar date as these changes in Chapters 3 & 5. Given that the main chapters of EU GMP normally apply to manufacture of finished products but that the scope of this proposed change (and that to chapter 5) appear to include both IMPs and active substances clarification is needed now on how the requirements in the new guideline on health based exposure limits should be used in relation to requirements on cleaning validation according to Annex 15 of the EU GMP.
The proposed GMP changes make it clear that introducing new products into a facility will require a toxicological risk assessment. There is no mention either in the cover note or the text if this change is expected to give rise to any associated license changes or not, e.g. will future authorisations for production plants be given per active material handled, would a facility change require documentation submission such as a toxicological study etc.

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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...."

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	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.
	lation/Guidance Document: The Rules Governing Medicinal Products in the European U		

Medicinal Products for Human and Veterinary Use, Part 1, Chapter 5: Production

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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 8: Complaints, Quality Defects and Product Recalls***

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General Comments
There are no general comments

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	Principle	The addition of certain words (i.e. assess and CAPA) to this paragraph will better reflect the introduction of QRM principles and make the section more effective.	Amend Principle to red: **"**In order to protect public and animal health, a system and appropriate procedures should be in place to record, **assess**, investigate and review complaints including potential quality defects, and if necessary, to effectively and promptly recall medicinal products for human or veterinary use and investigational medicinal products from the distribution network. Quality Risk Management principles should be applied to the investigation and assessment of quality defects and to the decision-making process in relation to product recalls, **Corrective and Preventative Actions (CAPA)** and other risk-reducing actions. Guidance in relation to these principles is provided in Chapter 1."
	8.2	Personnel involved should be trained and an assessment performed.	Amend 8.2 to read: "Sufficient **trained** personnel and resources should be made available for the handling, **assessment** investigation **and review** of complaints and quality defects and for implementing any risk-reducing actions. Sufficient **trained** personnel and resources should also be available for the management of interactions with competent authorities."

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	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	8.8 ii	Significance of distribution especially for temperature sensitive products has not been highlighted. (See also comments below which proposes new wording for items iii & iv and in which the reference to distribution in these sections has been deleted.)	Amend 8.8 sub-point ii, second sentence to read: "The checking or testing of reference and/or retention samples should be considered as part of this, and in certain cases, a review of the batch production record **and batch distribution record (especially for temperature sensitive products)** should be performed."
	8.8 iii & iv	It is to be expected that there will be a time framing for responding to a complaint and close out of a complaint. In this respect the severity of the complaint should be considered when setting this timeline.	Delete reference to distribution information in section iii and Amend 8.8 iii & iv to read: iii.The need to request a sample of the defective product from the complainant and, where a sample is provided, the need for an appropriate evaluation to be carried out. iv The decision making process that is to be used concerning the potential need for risk-reducing actions to be taken in the distribution network, such as batch or product recalls, or other actions. The assessment of the risk(s) posed by the quality defect **based upon severity and extent of the quality defect.**

	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	8.8 v.	Order to highlight the importance of notification to NCA	Amend 8.8 sub-point v to read: "The assessment of the impact that any recall action may have on the availability of the medicinal product to patients/animals in any affected market and the need to notify the relevant authorities **of such impact."**
	8.15	This section lacks emphasis on QRM principles	Amend 8.15 to read: "8.15 An appropriate level of root cause analysis work should be applied **based upon risk** during the investigation of quality defects. In cases where the true root cause(s) of the quality defect cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those **using a science and risk-based approach**."
	8.19	PQRs as a data source has not been included	Amend 8.19 to read: "Quality defect and corrective and preventative action records and **product quality reports (PQR)** should be reviewed and trend analyses should be performed regularly for any indication of specific or recurring problems requiring attention.

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	SECTION	COMMENT / RATIONALE	PROPOSED CHANGE (IF ANY)
	8.23	Agents or traders (brokers) involved in the distribution chain have not been included.	Amend 8.23 to read: "The batch/product distribution records should be readily available to the persons responsible for recalls, and should contain sufficient information on wholesalers, **distributors or third parties** and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches and amounts delivered), including those for exported products and medical samples."
	8.29	It is to be expected that a recall will have an official "close out". Recalls should be closed when the desired amount of product is recalled and a decision taken on recalled product is executed.	Amend 8.29 to read: "The progress of the recall process should be recorded **until closure** and a final report issued. Progress records and the final report should include a reconciliation between the delivered and recovered quantities of the concerned products/batches."