<Date of submission>

Submission of comments on '<EU GMP Part I Chapter 5 Production>'

Comments from:

Name of organisation or individual
LEEM

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)*

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)*
5.17		Comment: Depending on the country regulation, some veterinary products may be considered as "Pesticides" or "Medicinal products". It may therefore be confusing to take "Pesticides" as an example in this document Proposed change (if any): The production of technical poisons, such ~~as pesticides~~ and herbicides, should not be allowed in premises used for the manufacture of medicinal products.	
5.17		Comment: Some drugs have specific characteristics compared to the family they belong to. For example, some cancer drugs are not carcinogenic. It would be appropriate to include such distinction in the document. Proposed change (if any):	
5.17		Comment: Should a classification of already known risk products be established, with the recommended types of premises (dedicate/separate) to use? Proposed change (if any):	
5.18		Comment : "Robust design of the premises, equipment and processes" should be precised as possible.	

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		Proposed change (if any):	
5.18		Comment: Although the avoidance is the final purpose looked for, we can mainly work on the prevention. The text should be updated to reflect this situation Proposed change (if any): Contamination of a starting material or of a product by another material or product must be ~~avoided~~ prevented. This risk of accidental cross-contamination ~~arises~~ resulting 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, and from operators' clothing must be assessed. Since the ~~The~~ significance of this risk varies with the type of contaminant and of product being contaminated, these elements must also be considered in the assessment (e.g., . ~~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~~ prevented by robust design of the premises, equipment and processes which take place within a manufacturing facility. This should be supported by appropriate procedures and technical or organizational measures, including reproducible cleaning and decontamination processes of validated effectiveness.	
5.18		Comment:	

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		It would be good if the regulation could make a distinction between concept of "shared facilities" and "shared (non-dedicate) equipment". One could probably manufacture certain products within the same facilities, as long as the equipment for such product is dedicated and the conditions for cross contamination can be shown to be non-existent. For example, liquid production, or production within completely closed pieces of equipment.	
5.19		Comment: The toxicological evaluation should not be required for ALL products manufactured. It should only be required for most hazardous contaminants such as highly sensitizing materials (such as beta lactams), biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. (see also Chapter 3, 3.6) Proposed change (if any): text should be changed accordingly	
5.19		Comment: Proposed clarification in the text Proposed change (if any):	

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		Where the toxicological evaluation supports a threshold value, this should be used as an input parameter in risk assessment. The ~~A~~ Quality Risk Management approach should therefore assess this threshold value against ~~be used based upon this toxicological evaluation and~~ the potential cross contamination risks presented by the products manufactured. Factors including; facility/equipment design, personnel and product flows, 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.	
5.20		Comment : Wording clarification Proposed change (if any) : Supervision ~~Monitoring~~ of working behaviour to ensure training effectiveness and compliance with the relevant procedural controls.	
5.26		Comment: wording clarification Proposed change (if any): The selection, qualification, approval and maintenance of suppliers of starting materials, together with their purchase and acceptance of these materials, should be documented as part of the pharmaceutical quality system. The level of supervision	

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		should be proportionate to the risks posed by the individual materials, taking into account of their source, manufacturing process, supply chain complexity and the final use to which the material is put in the medicinal product.	
5.26		Comment: Can we get clarification of what is being meant by "the final **use** to which the material is put in the medicinal product"? Do we mean the role of the substance?	
5.26		Comment: Can we get clarification of what is being meant by the "/" in "The supporting evidence for each supplier **/** material approval"? is it the alternative or are we actually talking about the "Couple Supplier – material"?	
5.26		Comment: The whole paragraph "The quality requirements established by the manufacturer […]" must be moved under "Active substances" in section 5.27 and since this requirement must be limited to the most critical starting materials.	
5.27		Comment: We may not be able to achieve the requirement of traceability including the starting material for API bought to Third Parties since source of active substance starting material is described in the closed part of the dossier (EDMF, CEP). This requirement is related to responsibility of the manufacturer of active substances (EC GMP Part II section 7.1) Proposed change (if any): Supply chain traceability should be	

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		established and the associated risks, from active substance ~~starting materials~~ to the finished medicinal product, should be formally assessed and periodically verified. 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		Comment: The sentence 'For veterinary medicinal products, audits should be conducted based on risk' should be clarified	
5.27		Comment: Wording clarification Proposed change (if any):For veterinary medicinal products, audits should be conducted ~~based on risk~~ using a risk based approach.	
5.27		Comment: It should be indicated what the level of access would the regulator expected to the audit (audit report, corrective actions).	
5.27		Comment: Wording clarification Proposed change (if any): The report should fully reflect what was done and seen ~~on~~ during the audit with any deficiencies clearly identified. Any required Corrective and preventive actions should be implemented.	
5.28		Comment: Wording clarification	

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		Proposed change (if any): For each delivery of starting material the containers should be checked for integrity of package, including tamper evident seal where relevant, and for correspondence between the delivery note, the purchase order the supplier's labels and approved supplier information maintained by the medicinal product manufacturer.	
5.33		Comment: As a minimum identification testing should be performed: an identification test is not necessarily the most discriminating test. Proposed change (if any): As a minimum the most discriminating testing should be performed	
5.33		Comment: Responsibilities of intermediaries manufacturers should be defined in this paragraph.	
5.33 b		Comment: how to define an appropriate interval should be clarified. Proposed change (if any): The finished product manufacturer should perform audits at appropriate intervals defined by a risk-based approach at the sites(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.	

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5.33 c		Comment: If the designated person should ensure that the batch has been checked for compliance a certificate of conformity different of a certificate of analysis should be issued and signed or the certificate of analysis should refer to the formal agreement. Proposed change (if any): This person should ensure and asess in writing that each batch has been manufactured and checked for compliance with the requirements of the formal agreement.	
5.33 e		Comment: For non pharmacopeia test method, this full analysis can require an important analytical development that limits the interest of control delegation	
5.33 e		Comment: there is other method to check the reliability of supplier'analytical results when reducing in-house testing: Analytical transfer protocol and detailed review of the raw data is actually a strong process for delegation of control. According to the cGMP in analytical laboratory we can review all raw data and	

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		chromatograph or other graph which is a more accurate and detailed veriifcation of the analytical laboratory practices. By experience this give a lot information on the laboratory practices. Proposed change (if any): The finished product manufacturer should also perform appropriate control on laboratory results.	
5.42		Comment: wording in order to align wording with new 5.26 Proposed change (if any): The selection, qualification, approval and maintenance of suppliers of primary and printed packaging materials shall be accorded attention similar to that given to suppliers of starting materials.	
5.68		Comment: This Chapter (Product shortage due to manufacturing constraints) should be cancelled totally. It does not make sense in this Chapter. Proposed change (if any): cancel Chapter 5.68	

Please add more rows if needed.