PHARMIG
Verband der pharmazeutischen Industrie Österreichs

Vienna, 26 May 2014

PHARMIG response to the European Commission Draft:
EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use
Annex 15: Qualification and Validation

PHARMIG, the association of the Austrian pharmaceutical industry, would like to thank the European Commission for the opportunity to comment on the Draft Annex 15 of the EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.

When reading the document it is noticed that there are is a non-consistent use of the terms qualification (facilities and equipment) and validation (processes). A continuous terminology in agreement with these definitions is highly recommended.
Furthermore we would like to encourage to extend the glossary with some terms which are key to understand the text but not explicitly defined, such as 'complex validation projects'…

Please find following our specific comments on certain paragraphs of the document.

3.4 Equipment, especially if incorporating novel or complex technology, ~~should~~ may be evaluated at the vendor prior to delivery.
Comment: FAT activities are not under the umbrella of GxP regulations, but activities and documentation may supplement or replace validation documents as defined by the user.

4.20 Validation protocols should include, but are not be limited to the following:

…

e) List of the equipment/facilities to be used (including measuring/

~~f)~~ monitoring/recording equipment) together with the calibration status.

…

Comment: Formal remark, merge points e & f

5.2 It is recognised that ~~validation~~ verification of transportation may be challenging due to the variable factors involved however transportation routes should be clearly defined. For transport across continents seasonal variations should also be considered.

Comment: The terms qualification, validation and verification should be used consistently throughout the document.

7. ~~VALIDATION~~ QUALIFICATION OF UTILITIES

Comment: The terms qualification, validation and verification should be used consistently throughout the document.

7.1 The quality of media that are in contact with the product (steam, water, air, other inert gases, ~~coolants~~ etc.) should be confirmed following installation using the qualification steps described in section 3.

Comment: Coolants are not in contact with the product and therefore need not be qualified.

7.3 ~~A risk assessment should be carried out where there may be direct contact with the product e.g. HVAC systems or indirect contact such as through heat exchangers tomitigate any risks of failure.~~

Where utilities may have direct contact with product (e.g. HVAC systems) or indirect contact (e.g. heat exchangers), potential risks of failure and mitigation measures shall be identified through a risk assessment.

Comment: Revision is proposed to improve the clarity of wording of this paragraph.

8.3 *Where microbial testing of surfaces in clean rooms is carried out, validation should be performed on the test method to confirm that sanitising agents do not influence the result.*

Comment: The meaning of this passage is not clear: sanitising agents are used for disinfection and will always have an influence on microbial testing of surfaces.

9.5 ~~Limits for the carry over of product residues should be based on a toxicological evaluation to determine the product specific permitted daily exposure (PDE) value.~~ The justification of cleaning limits ~~for the selected PDE value~~ should be documented in a risk assessment which includes all the supporting references. The removal of any cleaning agents used should also be confirmed.

Acceptance criteria should consider the potential cumulative effect of multiple equipment in the process equipment train.

Comment: PDE is just one example for the determination of cleaning limits. The risk assessment shall serve as an instrument for that determination.

9.7 Where campaign manufacture is carried out, the impact on the ease of cleaning between batches should be considered and the maximum length of a campaign (in ~~both~~ time and/or number of batches) should be the basis for cleaning validation exercises.

Comment: Time and number of batches are not always equally important to ensure the cleanability or detectability of product residues after campaigns.

9.8 Where a worst case product approach is used as a cleaning validation model, the rationale for selection of the worst case product should be justified and the impact of new products to the site assessed. When there is no single worst case product when using multi-purpose equipment, the choice of worst cases should consider a

toxicological assessment ~~toxicity and PDE value~~ as well as solubility. Worst case cleaning validation should be performed for each cleaning method used.

Comment: PDE values are just one option to establish meaningful threshold values.

9.13 Where cleaning validation has shown to be ineffective or is not appropriate for some equipment, dedicated equipment may ~~should~~ be used for each product or other measures have to be taken to achieve cleanliness of the equipment concerned.

Comment: Clarify the text regarding the need for dedicated equipment. The use of dedicated equipment is not the only possible consequence.

~~11.1 The change process is an important part of knowledge management and should be handled within the pharmaceutical quality system.~~

Comment: Section 11.1 is redundant to the glossary of this annex and also respective EU GMP text. The statement therefore can be discarded.