<3/13/2018>

Submission of comments on Annex 1 of the EudraLex – Volume 4

Comments from:

AQPA (Austrian Qualified Person Association)
About aqpa: The Austrian Qualified Person Association (aqpa) was founded in 2008. Because of the unique responsibilities and tasks of a Qualified Person in Europe they need a forum to represent the Qualified Person in Austria. The aqpa provides Austrian Qualified Persons with a platform allowing them to exchange their experience, discuss the latest regulatory requirements, identify and address troubles and challenges and to support a harmonised European approach with a special focus on the specific Austrian national requirements. Today the Austrian Qualified Person Association is led by the following representatives from the industry: Georg Göstl (Chairman), QP, Shire; Gabriela Schallmeiner (dep. Chairwoman), QP, Inspection-Ready Consulting; Regine Tomasits (Secretary), QP, Boehringer Ingelheim, and Markus Thiel (Treasurer) , QP and Managing Director, Roche Austria GmbH. **Website:** www.austria-qp.at The Austrian Qualified Person Association appreciates the opportunity from the European Commission to comment the Draft of Annex 1.

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)*
	The implementation of the new requirements will require changes of processes and practices. The document should specify a transition period of minimum 24 months during which manufacturers will perform gap analyses and define action plans to meet the revised guidance.	
	Some principles could be used for non-sterile manufacturing. However, Annex 1 should be restricted to manufacture of sterile products. A company which is only manufacturing non-sterile products will not refer to an Annex for sterile manufacture.	
	The draft guidance lacks homogeneity which might lead to confusion and misinterpretation. It is recommended to revise the entire document for consistency and accuracy of wordings and definitions.	
	It would be helpful to clarify the terminology and verbiage around "cleaning process, sanitization, disinfection, sterilization / in sterile state" throughout the document	
	The terms "should" may be interpreted as "must" by inspectors from different authorities. It is recommend to clarify the exact meaning of these terms in the final document	
	The draft seems to prefer an emphasis on quality control and testing rather than design, validation and sterility	

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	assurance programs. The detailed requirements might impede implementation of new methods and processes.	

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)*
Line 159-164		Comment: section f) should be removed, since it does not add value to this document. However, if it should remain for certain reasons, we recommend to add the missing word "for" in the sentence and adopt the wording to the responsibility of the Qualified Person. Proposed change (if any): Revise to, "The QP responsible for the quality release…"	
Line 188-194		Comment: Personnel working in a grade A/B cleanroom is trained on sampling with contact plates and air sampling. Personnel in "such areas" meaning critical areas of production are qualified and trained, but not necessarily in sampling of operator's bioburden. It is recommended to use consistent verbiage (e.g. contact plates or glove prints as in table 6, rather than using new terms like "operator's bioburden")	
Line 197-200		Comment: visual assessment of compliance with aseptic gowning procedures might be difficult in specific situations, where only one person is allowed in the airlock.	
Line 200-203		Comment adapt wording Proposed change: Only trained personnel assessed for their correct gowning should be authorized to enter any grade A/B area. Operators must have participated in a successful APS test, during which they performed their normal duties in order	

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		to be allowed to perform aseptic operations whilst unsupervised.	
Line 236-237		Smart phones or tablet computers are essential tools also in CNC, C or D areas. Proposed change: "Wristwatches, make-up and jewellery should not be allowed in clean areas. Other personal items such as mobile phones should not be allowed in A/B areas.	
Line 253-256 Line 258-261		Comment: Disinfected shoes would require Disinfectant Efficacy Testing for shoe material/s per definition for "disinfection" (e.g. according to USP <1072>) Proposed change: Change to "… appropriately sanitized shoes…"	
Line 299		Smoke studies should be used for training of operators to demonstrate impact on aseptic technique in dynamic vs. static state	
Line 351		Comment: adapt wording Proposed change: Materials liable to generate fibres should not be permitted in A/B areas and in grade C where open product is exposed to the environment.	
Line 425-426		Comment: The pressure differences should be recorded regularly or otherwise documented. What does "otherwise documented" mean?	
Line 474-477		Comment: Unclear wording, does it means all of the tests (visual, mechanical and physical) have to be performed at the	

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		beginning and end of a batch, and following any intervention? Any tests might be performed at the beginning and at the end. Following interventions, glove testing might only be required in situations where the intervention may have an impact on the integrity of the unit. Furthermore: what is meant by "mechanical" tests? Proposed change: delete the word "mechanical" since this would be part of the physical tests.	
Line 505		Comment: Table 1: It appears that the title/header of the 4th column of the table is incorrect. Proposed change: The title of column 4 should read "ISO classification at rest/in operation", to correspond to columns two and three, respectively.	
Line 540-545 and Line 1588-1590		Comment: Table 2 provides limits for settle plates in grade C/D area. However, it is not clear if this is necessary for grade C/D areas which do not pose risk to the process. Proposed change: Add footnote that the use of settle plates in grade C/D area needs to be assessed using a risk assessment considering the risk to process.	
Line 558-561		Comment: The requirement is more restrictive than before and not aligned with ISO-14644 without an opportunity to apply QRM principles for any different time periods.	
Line 567		Comment: Looks like this session deals with disinfection of facility. What is the difference between disinfection and	

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		sanitization? Is there another session on sanitization? Proposed changes: recommend delineating what Annex 1 refers to when it speaks to "Disinfection". Will the appropriate use of sterile sanitizers, sanitization of equipment, or personnel be discussed elsewhere in Annex 1? Recommend to add definition for disinfection and sanitization, and align with existing definitions as e.g. per USP <1072>. Disinfection typically requires establishing DET (disinfection efficiency test) data on the specified surface.	
Line 580-583		Comment: Requirements for disinfectants are given "to be monitored for microbial contamination" and use in grade A/B "to be sterile prior to use". However, the word "monitored" gives a lot of room for interpretation. Is a specific testing in the microbiology lab prior to use required or is a proof of certificate from a qualified vendor sufficient? Proposed change: Provide more clarity about "to be monitored for microbial contamination" and test methods to be applied (if applicable).	
Line 597-598		Proposed change: Process related alarms should be reviewed and approved and evaluated for trends.	
Line 619		Proposed change: All critical surfaces that come into direct contact with sterile materials should be sterilized.	
Line 623		Proposed change (if any): Their return to use should be approved by the quality unit.	

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Line 703		Replace "Include all outlets" by" include all **critical** outlets"	
Line 705		Comment: A water system could be used many times per day, there is no need to take a sample each time it is used. Proposed change (if any): Revise to have a time boundary (e.g. every working day).	
Line 715-716		Comment: For pure steam generation, purified water with a low level of endotoxin should be used. As the pharmacopeia monographs do not require endotoxin testing or limits for PW, the expectation is not clear. Proposed: Delete "low level of endotoxin" or otherwise provide clear guidance.	
Line 797		Comment: 'Residual risks should be justified.' Line 148 –150 already describe the risk assessments and residual risk. In order to make the document clean, please remove this sentence here. Proposed change (if any): Please remove 'Residual risks should be justified.'	
Line 814 -816		Comment: Table 4: Examples of operations … For Grade B, it states "removal of sealed product from the Grade A zone." Sealing of product may be performed outside of the Critical zone under Grade A air supply (see clause 8.21 and 8.22). The surrounding environment for such activity is typically Grade C or D. Therefore the sealed product would be removed from a Grade C zone, not Grade B. If the product is	

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		sealed, then there is no impact to the sterility of the product and it does not need to be removed from the Grade B zone. Proposed change: Remove this example from Grade B operations in Table 4, or provide additional information for what type of process would require removal from the Grade B zone.	
Line 888-889		Comment: a statistically valid sampling plan would result in large numbers of containers to be tested. Proposed change: delete the sentence "A statistically valid sampling plan should be utilized."	
Line 931-932		Comment: Due to the probabilistic nature of visual inspections, an adapted wording is proposed. Proposed change: Critical defects identified during subsequent sampling of acceptable containers should trigger an investigation.	
Line 944-946		Comment 1: The use of the term "sensitivity" may be mistaken as sensitivity in terms of defect size, i.e., particulate size or the overall defect rate. The statement should suggest the "detection capability." Otherwise, it may be understood as if the manual inspector can detect 100 micron particulate, the automated inspection should be able to detect 50 micron particulate. Which is a very different statement altogether. Proposed change (if any): A clarification of "sensitivity" is	

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		needed here or simply state that automated methods should be equal or better than manual inspection methods. Comment 2 on sentence "Where automated …. Prior to start up and at regular intervals" Actually, Whole system checks should follow a schedule of testing at regular intervals. This is to be defined and justified by equipment qualification and should take into consideration specificity of the defects seen in the material being tested.	
Line 948-951		Comment: Inconsistent language in this clause. Does "level" also mean "reject rate" or are these two different attributes? The use of defect "level" is also discussed in clause 8.26 (Line 927), and it is not clear if this also can be used synonymously or interchangeably with "reject rate". If reject rate and reject level are synonymous, then clause 8.29 (Lines 949-950) is redundant to clause 8.26 (Lines 922, 926-929) with regard to trending and investigations. Proposed change: please use consistent terminology so as to be clear on the intent. Please remove any redundant text.	
Line 1020-1021		Comment: delete requirement of storing sterilized items in at least grade B, since this is not suitable e.g. with isolators in grade C or D surrounding	
Line 1331–1334		Comment: The use of on-line pre-filtration integrity testing may in some specific cases actually increase the risk for the sterility of the product due to technology and manipulations required, independent of batch sizes. In order to integrity test	

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		a filter, the test must be performed at atmospheric pressure. This may allow the integrity of the sterilized filter to be compromised and is in direct conflict with the last sentence of clause 8.63, where it states that once a system has been sterilized by SIP, it should remain integral prior to use. In addition, drains are prohibited in Grades A/B (clause 5.8), and as such, it may be impossible to integrity test the in-line sterilizing grade filter after it has been sterilized based on facility design and the process. Proposed Change: The pre-use integrity test is recommended; however, in cases where the integrity of the sterilized filter may be compromised by performing a filter integrity test post SIP of the filter due to design considerations, a pre-SIP filter test together with the post-use filter-integrity test must be justified to verify the integrity of the filter. This should be independent from batch size.	
Line 1460—1461		Comment: The frequency for sterilization of lyophilizers should be risk based depending upon the equipment and process.	
Line 1615-1619		Comment: Unclear what "pre-disinfection" means, as outside of operations is at-rest which means "post-disinfection".	
Line 1659-1662 Line 1703-1705		Comment: How often should the monitoring of 5 µm particles be taken? Continuous or periodic in the isolator and rRABS? Proposed changes: recommend to provide guidance on the monitoring frequency of 5 µm particles in the critical area. Should they be monitored at the same interval or continuously	

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		as for 0.5 µm particles. Also, provide guidance for all other areas (e.g. not critical) to be clear on expectation.	
Line 1835 – 1836		Comment: Statement about bracketing or matrix approaches is not clear. Bracketing or matrix approach should be applicable not only for initial validation, but for the routine process simulation program as well. Also it is not clear by what is meant of the same container/closure configuration, as a bracket approach may encompass multiple container/closure configurations. Proposed change (if any): Reword to state "Bracketing or a matrix approach can be considered for initial validation as well as the subsequent routine process simulation program to encompass representative container/closure combinations"	
Line 1886		Comment: For a multi-product facility, what is the definition of an "aseptic process"? Is the aseptic process representative in terms of container/closure, e.g. one APS per year of 20 mL vial size and one APS per year of 2 mL vial size? Proposed change (if any): Provide clarification or allowances for a bracketing approach to bracket worst-case conditions such as container-closure size, etc., as it is impossible to perform media fills every six months for all configurations. Recommend to require documented assessment for selection for bracketing.	
Line 1891-1894		Proposed change: add an additional point for semi-manual	

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		filling: For semi-manual filling operations each container closure and equipment train should be revalidated using a bracketing or a matrix approach and operators should be revalidated annually.	

Please add more rows if needed.