EU-GMP ANNEX 15 "Draft of 06.02.2014' - COMMENTS of the German Expert Group 10 "Qualification/Validation"
Comment sent to ADM-GMDP@ema.europa.eu and sanco-pharmaceuticals-D6@ec.europa.eu by End of May 2014

Comment No.	Section of Doc.	Comment	Comment made by	Date	Outcome
1	Principle	According to the first sentence Annex 15 is not valid for API´s therefore the reference to ICH Q 11 does not make sense.	Expert Group 10	22 May 2014	
2	General	Since Annex 15 is not intended to cover APIs therefore the reference to ICH Q 11 does not make sense. (see comment 1)	Expert Group 10	22 May 2014	
3	1.3	The sense of the sentence is not clear, it is proposed to delete it.	Expert Group 10	22 May 2014	
4	1.5 j	In this sentence revalidation is mentioned for the first and only time. But there is no comment in the glossary about this topic or at any other point in the text. Here we see danger of misunderstanding and we recommend clarification about the meaning. *Recommendation for redrafting for clarification and to avoid misunderstanding:* *… revalidation after changes …*	Expert Group 10	22 May 2014	
5	2.4	Here information about sampling and testing is missing. *Recommendation for redrafting:* *A written validation protocol should be prepared which defines the critical systems, attributes and parameters which are important ~~and,~~ scientifically based on pharmaceutical development the acceptance criteria for each, and the methods of sampling and testing.*	Expert Group 10	22 May 2014	

6	3.2	From point of view of the Expert group 10 it shall be clarified, that there is necessity for creation of a URS for all (not just new) facilities, systems and equipment. *Recommendation for redrafting:* *The specification for ~~new~~ facilities …*	Expert Group 10	22 May 2014	
7	3.3	From point of view of the Expert group 10 it shall be clarified, that there is necessity for creation of a DQ for all (not just new) facilities, systems and equipment. *Recommendation for redrafting:* *… in the validation of ~~new~~ facilities …*	Expert Group 10	22 May 2014	
8	3.8	From point of view of the Expert group 10 it shall be clarified, that there is necessity for creation of a IQ for all for all (not just new) facilities, systems and equipment.	Expert Group 10	22 May 2014	
9	4.3	'Continuous verification' refers to validation, not to development. *Recommendation for redrafting:* *Medicinal products may be developed and processes may be validated using a traditional approach or a continuous process validation ~~approach~~; however irrespective of the approach used, processes must be shown to be robust and ensure consistent product quality before any product is released to the market.*	Expert Group 10	22 May 2014	
10	4.5	The section should be deleted, having in mind that compliance with MA is a general requirement, not just for 'legacy' products.	Expert Group 10	22 May 2014	
11	4.5	From our understanding "legacy" is an American term. This is not explained in the glossary.	Expert Group 10	22 May 2014	

12	Chapter 4	*The wording of the heading should get harmonized with the "Guideline on process validation for finished products - information and data provided in regulatory submissions" of the EMA.* *Recommendation for redrafting:* *Heading before 4.16 "Traditional process validation".* *Heading before 4.21 " Continuous process validation"* *(see also comment 16)* *Heading before 4.24 " Hybrid approach"*	Expert Group 10	22 May 2014	
13	4.14	Wording „strong risk-benefit“ is misleading: If there is advantage for the patient meant by this, than the term “positive benefit-risk ratio” would be better. *Recommendation for redrafting (May be clearer for non-native speakers):* *In exceptional circumstances where there is a strong ~~risk –~~ benefit to risk ratio to the patient,*	Expert Group 10	22 May 2014	
14	4.14	In the Validation Master Plan there should be described the decision to perform concurrent validation. The demand of the Finnish colleagues is supported to document this decision in the validation protocol. In the validation protocol there should be documented in each case the decision about pre-release of certain batches before finish of the validation. *Recommendation for redrafting:* *However, the decision to carry out concurrent validation must be justified, documented in the VMP and approved by authorised personnel*. *The procedure to release batches prior to completion of the validation programme must be clearly documented and approved.*	Expert Group 10	22 May 2014	

15	4.20	From the validation protocol there should be identifiable, which risk analysis was used as basis for definition of the amount of validation tasks. For clearness here should be linked to the Master Batch Record. *Recommendation for redrafting:* *Validation protocols should include, but are not be limited to the following:* *(a) A short description of the process and a reference to the respective Master Batch Record.* *(b) a reference to the risk assessment where CQAs and CPPs have been identified and evaluated* *(c) Summary of the CQA's to be investigated*	Expert Group 10	22 May 2014	
16	4.24	4.24 should get an own subtitle „*Hybrid approach*" instead of being mentioned in the framework of continuous process verification to make sure being in line with the EMA-Guideline on process validation for finished products (section 5.3 "Hybrid approach"). We assume that most pharmaceutical manufacturers will start with a hybrid approach first and not with an overall new and sophisticated enhanced approach.	Expert Group 10	22 May 2014	
17	Ongoing Process Verification during Lifecycle (4.25 - 4.29)	The rationale and benefit of this section is not clear at all. Manufacturers performing a continuous process verification will not have to carry out additionally an ongoing process verification. Manufacturers performing the traditional process validation have at least carried out three validation batches. All manufacturers have to do PQR periodically. If the terminology "ongoing process verification" is used instead of "revalidation" the rationale of this section has to be addressed.	Expert Group 10	22 May 2014	
18	4.28	What is meant by „incremental changes"? A comment in the glossary or more distinct wording would be helpful.	Expert Group 10	22 May 2014	

19	5.2	According to GDP (point 9.4) this is additionally valid for transports, which are not performed across continents. Proposal: to delete the sentence. *Recommendation for redrafting:* *~~For transport across continents~~ seasonal variations should also be considered.*	Expert Group 10	22 May 2014	
20	5.4	Wording *Recommendation for redrafting:* *~~Due to the~~ If variable conditions are expected during transport, e.g. …*	Expert Group 10	22 May 2014	
21	7.1	All media with direct contact to the product shall be validated. For use of coolants a direct contact to the product is doubtful. *Recommendation for redrafting:* *The quality of steam, water, air, other inert gases~~, coolants and~~ other media in potential contact with the product ~~etc.~~ should*	Expert Group 10	22 May 2014	
22	8.1	That means that the validation of routine analytical methods and of monitoring methods is not regulated by Annex 15. *Recommendation for redrafting:* *All analytical test methods used in qualification, validation or cleaning exercises should also be validated with an appropriate detection and qualtification limit, where necessary, as described in Chapter 6 of the EU-GMP guide Part I for routine analytical methods.*	Expert Group 10	22 May 2014	
23	9.2	If it is technical feasible visual check shall be performed in each case (replace “may”). *Recommendation for redrafting:* *If practically feasible, ~~A~~ a visual check for cleanliness ~~may~~ should form ~~an important~~ part of the acceptance criteria for cleaning validation however, …*	Expert Group 10	22 May 2014	

24	9.3	…and a decision about release of future batches has to be considered in the protocol and in the frame of assessment of data. *Recommendation for redrafting:* *The level of data from the verification to support a conclusion that the equipment is clean should be ~~evaluated~~ defined in advance.*	Expert Group 10	22 May 2014	
25	9.5	The fact should be faced that the vast majority of executed cleaning validations are based on the 1/1000 dose, 10 ppm and/or visually clean criterion, not on PDE. The annex should at least allow for a transition period where the traditional cleaning validations remain acceptable. *Recommendation for redrafting:* *… all the supporting references. As long as a PDE-concept is not implemented, it is possible to perform on the base given by e. g .1/1000 dose 10 ppm criterion*	Expert Group 10	22 May 2014	
26	10.3	This demand was already documented elsewhere. Furthermore check of process effectiveness is not correctly assigned to Re-Qualification. Proposal: assign to point 9. The impression should be avoided, that confirmation of process effectiveness is necessary only for manual processes. *Recommendation for redrafting:* *Where manual processes are used, such as for cleaning of equipment, ~~the~~ continued effectiveness of the process ~~should be confirmed~~ at a justified frequency is of particular importance.*	Expert Group 10	22 May 2014	

27	Glossary "Cleaning Validation"	Definition is assessed as insufficient, as there is no advice to cleaning agents and similar topics. *Recommendation for redrafting:* *Cleaning validation is documented evidence that an approved cleaning procedure will remove all traces of the previous product, of cleaning agents used, and of other possible contaminants, e.g. microbiological, in the equipment, to an acceptable level.*	Expert Group 10	22 May 2014	
28	Glossary "Traditional approach"	The definition does not provide a clear distinction to the enhanced approach and refers only to development, not to the likewise 'traditional' n=3 validation. It is proposed to delete the definition completely, given that – the traditional development approach is described extensively in ICH Q8 (R2) – the traditional validation approach is already defined in section 4.16 of this document	Expert Group 10	22 May 2014	
29	Glossary "Continuous process verification"	*Adapt to the heading before 4.21* *Recommendation for redrafting:* *" Continuous process validation"*	Expert Group 10	22 May 2014	

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