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Submission of comments on 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, Annex 16 – Certification by a Qualified Person and Batch Release

Comments from: APIC

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1. General comments

General comment
APIC supports the Revision of Annex 16 of the EU Guidelines for good manufacturing practices to give improved guidance on batch certification and release by the Qualified Person. Notwithstanding there will be a strong need to harmonize requirements and interpretations over the member states to assure that the same requirements (no additions – no modifications) are applied over the different member states.

2. Specific comments on text

Section number(s) of the relevant text	Comment and rationale	Proposed changes
Section 2: General principles		
2.2	It is stated that the batch should be *"…manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member state …"* The expression "*equivalent"* should be defined	
2.3.2	Needs alignment in wording with other sections like with 2.4.2. 2.3.2 states "*EU GMP or equivalent*" but in 2.4.2 the word "*equivalent"* is omitted	Harmonization throughout the document is needed
2.3.3	"*This is the final step in the process which effectively releases the batch for sale or export*." As a batch can be released for both cases sale within the manufacturing country and for export. Even for sale within EEA it is an export.	"*This is the final step in the process which effectively releases the batch for sale and/or export*." Harmonization is recommended throughout the document see 3.1
	"*This could be done by the QP as an integral part of certification or it could be done afterwards by another person*." Who could perform the release by delegation of the QP should be a qualified person form QA/QC area	"*This could be done by the QP as an integral part of certification or it could be done afterwards by another quality qualified person*."
3.2	*"The QPs should be able to demonstrate knowledge of the product type, production processes, technical advances and changes to GMP".* Definition of "*technical advances" is needed.*	

Section number(s) of the relevant text	Comment and rationale	Proposed changes
	"Changes to GMP" is too broad. Not all GMP changes have impact on the product certification and / or quality	We recommend to change to: "… *changes made in the manufacturing process or testing*"
3.2 (cont.)	The expectation that the QP has also detailed knowledge of all processes and changes at all facilities involved in manufacturing is not realistic – this should be limited to "detailed knowledge of the steps they carry the responsibility for"	
3.3	"Manufacturing steps performed at sites in the EEA" To avoid misunderstandings we believe that steps here means intermediates.	we recommend to change to *"Manufacturing steps/intermediates performed at sites in the EEA*"
	This section also leaves open the possibility to hire a QP on consultancy basis – better to have a QP named and identified on the manufacturing license	
	" … *QP has access to the necessary details of the Marketing Authorisation to facilitate declaration of compliance."* A template of the declaration of compliance to be used throughout of the EEA is recommended.	
3.4.1	See 2.3.3	
3.5	Harmonization with 2.3.3 is recommended	
3.5.3	In order to maintain and provide transparency the certification of a medicinal product is recorded by the QP in a register, the text should be rephrased to also allow the use of a validated electronic register	"Certification is recorded in a register or equivalent document. *Electronic form can also be used if in compliance with Annex 11"*
3.5.5	Additional clarity is needed to describe the entire supply chain to the QP – a format proposal would be helpful	

Section number(s) of the relevant text	Comment and rationale	Proposed changes
	“The entire supply chain of the medicinal product, starting from the manufacturing sites of the starting materials and components, and including all parties involved in any manufacturing”	“The entire supply chain of the medicinal product, starting from the manufacturing sites of the starting materials components, packaging and including all parties involved in any manufacturing”
3.5.9	“*The active substances used in the manufacturing of the finished products have been manufactured in accordance with GMP and, where required, imported and distributed in accordance with …”*	The active substances used in the manufacturing of the finished products have been manufactured in accordance with GMP and, where required, imported stored and distributed in accordance with …
	It should be more clearly outlined that this paragraph refers to GDP’s for API’s	
3.5.17	The term adverse trend is not commonly used in API manufacturing, propose to replace by “out of trend”	
3.8.1	Bring in line with 3.5.3 and include the validated electronic register	
4	In global organizations independent certified enterprise regulatory compliance auditors can be used for self inspections and deliver reports for the QP statement	
4.1/4.2.3/4.2.5	"Outsourced activities" should be defined. Many APIs and excipients are purchased by the MIA holder from manufacturers selling these products to multiple customers based on standard specifications (usually called "purchased" APIs or excipients). The referenced Chapter 7 of the EU GMP Guide is focussed on "contract manufacturing", however, chapter 4 of Annex 16 presumably should cover such "purchased APIs" as well.	

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5.1/5.2/5.3	Whereas 5.1 explicitly mentions APIs and excipients (besides the finished products), paragraph 5.2 refers to finished product only, and 5.3 does not specify at all. Clarification is requested which deviations the QP needs to aware of. From the API/excipient manufacturers' perspective - unless the product is "contract manufactured" - it would be an extreme burden to inform each single customer of a "purchased" API/excipient about each and any deviation. It should be considered that generic APIs or excipients are sold to multiple customers, partly more than 200 throughout Europe. The QP should qualify his API/excipient suppliers, and the qualification (and audit) should cover the supplier's Quality System including the deviation handling process. The result of the qualification process (and audit) should provide the QP a sufficient level of trust in the supplier's processes, so that he may be confident that the supplier assesses and documents deviations in an appropriate manner. Consequently, paragraph 5.3 should refer to finished products or "contract manufactured" APIs or excipients only.	
5.2.2	“Adverse effect” brings the focus to patient safety what is not the initial intent of this sentence – this should be quality and efficacy related, propose to change in “negative effect”	
5.1/5.2.1	We suggest to delete "unplanned" and "unexpected". Rationale: a "deviation" is always unplanned or	

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	unexpected versus a "change" that is planned and may be permanent or temporary (the latter is called "deviation" by some people).	