29th May 2014

Submission of comments on EudraLex Volume 4 GMP - Annex 15: Qualification and Validation

(EMA/…/…)

Comments from:

Name of organisation or individual
comes compliance services, Ravensburg, Germany

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).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	CCS welcomes the revision of Annex 15, which defines Qualification and Validation (and/or Verification) activities for processes (process steps, activities, and process items). We would like to state the following comments:	
	There are several definitions and terms used in different context and meanings. ○ Activities such as Validation, Qualification and Verification (and Re-Qualification) ○ Applicable to facilities, equipment, utilities, cleaning, premises, product, processes etc. ○ Related to product, process, validation and system life-cycles In general we would like to suggest defining all used terms and definitions more precisely and unambiguously throughout the entire document. In general "Processes" contain several process elements or items, such as equipments (incl. usage e.g. dedicated or cleaning), facilities, utilities, materials (incl. movements and storage), computerized systems, locations (premises), and so on. The term "Process" should be defined as a set of	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	interrelated or interacting activities which transforms inputs into outputs through different process steps (e.g. cleaning ,weighing, filling, blending, transportation, packaging, etc.). Processes areas are mapped to different areas like production, laboratory, quality assurance, storage and include the material, samples, personnel, and data flow. Such processes can be documented and analysed by different tools, charts, diagrams and methods, e.g. Value Stream Mapping, Sankey, Process Analysis, etc. Processes can be executed and controlled internally or externally by a qualified third party (ref. EU GMP Chapter 7 / requires Quality Agreements). In general a process should be validated product-specific from the initial process start (incoming materials, procurement) to the finished pharmaceutical product incl. distribution ("last mile") – supply chain. Processes should be designed to product-specific attributes and parameters, irrespective of the validation or qualification approach (QbD / traditional / concurrent etc.); linking product(s) to processes to manufacturing. A comprehensive process management concept (incl. material flow analysis) is required for process validation. This can be documented into a Validation Master Plan or any other document / record according validation procedures and policies. In any case the level of validation or qualification (and/or verification) of process items and steps should be based on a risk-based analysis between the product and process elements.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Within pre-defined ranges process steps may be qualified for several and different combination of products. If they can be monitored and controlled verification might be applied. Based on ICH Q11 an "Overall Process Development Summary" is described including the action of "Linking Material Attributes and Process Parameters". The current Guideline on Process Validation (Final; Feb. 2014 - EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), Annex 1 defines a Process Validation Scheme. The requirement might be states like: *For critical processes an up to date process description / process map detailing the process steps, process items and flows like facilities, premises, utilities, equipments, physical and logical arrangements, data flows and interfaces with other systems, products or internal or outsourced processes should be in place.* Irrespective of whether or not validated processes are described textual or in the format of a comprehensive diagram all quality or product critical attributes and process elements (if named to an equipment, utility, facilities etc.) impacting (controlling, recording, settings) product quality should be defined and used to determine for each element the level of required compliance proof (validation, qualification and/or verification). Such a process map / reference model / process	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	summary can be included to a so called Validation Master Plan. ISO/IEC 15504-2 identifies for example process attributes (PA) as part of a Process Reference Model. Such process attributes would cover facilities, equipment, utilities, premises, computerized systems, equipment, or however any physical item would be named. Also process attributes can cover materials or activities, like cleaning or transportation. Also computerized systems as a special type of an process item should be validated according Annex 11. According ICH Q11 - Overall Process Development this is defined in the chapters: Summary and Linking Material Attributes and Process Parameters. In the EMA Note for Guidance on Process Validation from 2001 and the current EMA Guideline on Process Validation, Annex 1 defines a Process Validation Scheme. The current Draft Version of Annex 15 is based on the same structure as the current revision. Maybe re-structuring would make sense in terms of the overall setup. **The current Draft contains for Example:** Principles Section (Annex 16 – draft) defines "qualification and validation which are applicable to the facilities, equipment, utilities and processes" and Section "General" states that validation and qualification should be based on a justified and documented risk assessment of the facilities, equipment, utilities and	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	processes. Section 1.1 states that all qualification and validation activities should be planned and take the life cycle of equipment, process and product into consideration. The related Glossary section of Annex 16 defines life of a product, equipment or facility. The Glossary of the QWP Guideline for Process Validation states: The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly… ➔ Both terms in each glossary should be identical. Preferred would be the one in the Guideline. Section 3.2 (URS) defines specification for new facilities, systems or equipment. In addition EU GMP Chapter 3 – 3.34 to 3.44 defines "Premises and equipment". Section 2.4 defines a written validation protocol should be prepared which defines the critical systems, attributes and parameters. ICH Q9 (referenced in the fist section) defines for the product lifecycle: In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. The „potential applications for QRM" Annex II. No. 4 defines the Quality risk management for facilities, equipment and utilities / computer systems and	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	computer controlled equipment. The EU GMP Glossary EudraLex 4 defines VALIDATION as: Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification). QUALIFICATION is defined as: Action of proving that any equipment works correctly and actually leads to the expected results. The word validation is sometimes widened to incorporate the concept of qualification. ➔ The term Verification is now used in several sections, without defining it precisely in the Glossary or the Annex. EU GMP Annex 11 states that the application should be validated; IT infrastructure should be qualified. It was definitely the intention to move away from a purely system-based thinking / approach towards an application – process related. ➔ Annex 15 Draft is using the term "system" or "equipment" in several different meanings. Equipment (e.g. scanners, label printers) might be part of a qualified IT Infrastructure, as part of a validated process item. Also Annex 11 is referenced;	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	it does not correlate to it. ➔ **There is a confusing mix-up of terms and definitions for systems, facilities, equipment etc. through different "life cycles" and activities (validation, qualification, verification), which are even not aligned with the referenced documents in the chapter "Summary of changes"** ➔ This may lead to misinterpretations or misunderstandings	
	Section 1.1: Processes should be validated; process items and steps should be qualified and take the life cycle of product into consideration. Risk management should be applied throughout the lifecycle of the product taking into account patient safety, data integrity and product quality. As part of a risk management system, decisions on the extent of validation, qualification (or verification) and data integrity controls should be based on a justified and documented risk assessment of the entire process.	
	Section 1.3: Reporting requirements not required to be defined – responsibilities are defined in EU GMP Chapter 2 (revision 2014). Check duplication of content.	
	Section 1.4: delete "site"	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Also there might be not the need of defining a required document like a VMP; the SMF in Section 6.2 must define the validation strategy and methodology. A SOP (instruction type) should be the basis for a VMP (record/report type acc. Chapter 4). The characteristics or expected content should be defined – the given title of the document is irrelevant or the following phases like IQ,OQ,PQ. In Annex 11 it was avoided to use such common but differently understood wordings and definitions.	
	Section 1.5: The expected content of the VMP is correct, but there are different understandings of such elements. For c) "Summary of the facilities, systems, equipment, processes on" it might be preferable to state that all process steps and process items must be listed. It is not clear if the VMP is process- or product-related. The content and scope may be different for a production site if manufacturing 4 or 400 different products or variants. For i) "assessment of the resources required" can also be placed into a project / program plan. It is not directly	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	related to process validation – refer to Chapter 2 – 2.1 "adequate and appropriate resources" (duplication) For j) contains undefined terms of revalidation and / requalification (and "or" is missing) – section 10 contains re-qualification, but not revalidation. *Process validation should not be viewed as a one-off event. A lifecycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production (Ref. QWP process val.).* ○ *This implies the need for requalification and revalidation, change control etc. through the development, product and process life cycle.* ○ *Approach might be a staged one, bracketing, traditional etc. – based on a risk management concept / analysis* In general and however process validation is setup or documented (VMP, SOPs etc.), there might be the need to define that a SOP for "process management" must be in place. Annex 16 (DRAFT) requires for the entire supply chain	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	document should preferably be in the format of a comprehensive diagram (section 3.5.5.). There should be a clear structure from SMF, VMP, Specification Files and supply chain diagrams.	
	Section 1.6: A definition like "it may be necessary" is not expected in a regulatory document.	
	Section 2.5 Where validation protocols are supplied by a third party, - Refer to EU GMP Chapter 7 - Contract Giver and the Contract Acceptor - 7.4 The pharmaceutical quality system of the Contract Giver should include the control and review of any outsourced activities. ➔ This applies to all outsourced activities, process steps, items or documentation. ➔ Should be covered by formal agreements or Quality Agreements etc. ➔ Referred also to EU GMP Chapter 2 consultants	
	Section 2.8: "The conclusions of the validation should be reported and the results obtained summarised against the acceptance criteria." ➔ Acceptance criteria are CPPs and CQAs, as a result of linking them and proofing on process levels.	
	Section 3.2: User requirements specification (URS) URS is a very traditional term and might be not clear enough. These are not really "User" requirements, this are product, process (steps) and process items	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	requirements. Basically we see it as a three layer set: ➔ Product Requirements from e.g. Design Space, Overall Process Development Summary or Product Specification Files ➔ Process Requirements derived from Product Specs. ➔ Process items (equipment, facility, etc.) requirements- technically oriented It is stated that "The URS should be a point of reference throughout the validation life cycle". There are different definitions of life cycles: product, process, validation, system, and basically data life cycles. In this section the validation life cycle was used – but it is not also a point of reference throughout the product or at least process life cycle.	
	In Section 5. VERIFICATION OF TRANSPORTATION - It is recognised that validation of transportation may be challenging… ➔ The statement that this is challenging is not expected in a GMP Annex document. ➔ The activity or characteristics of "verification" is not defined and might be understood as an underlying and reduced qualification activity. ➔ Transportation is a process step a validated process in total. ➔ Transportation Verification on the basis of a risk	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	assessment within pre-defined ranges and continuous process monitoring and verification	
	Section 6. is named to VALIDATION OF PACKAGING, also section 6.2 states a Qualification of the machine settings. Section 7. VALIDATION OF UTILITIES (given example HVAC) ➔ Packaging is a process step, utilities are process items. Maybe restructuring of the Annex might be useful.	
	Section 10. RE-QUALIFICATION might be understood only to qualification, but not validation and/or verification.	
	Glossary: Lifecycle – All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use. in several sections there is the use of product, process and even "validation lifecycle" /section 1.3, 2.1, 3.2 Annex 11 Life cycle: All phases in the life of the (added: computerized) system. Lifecycle: All phases in the life of a product from the	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	initial development through marketing until the product's discontinuation (ICH Q8). Cross-check to EU GMP Chapter 4 shelf-life and retention of documents – retention of equipment required.	
	Section 10.1 Facilities, utilities, systems, equipment should be evaluated at an appropriate frequency to confirm that they remain in a state of control. Cross-check to Annex 11 – section 11. Periodic evaluation and Section 11 - change control – useful.	

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)*
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	
		Comment: Proposed change (if any):	

Please add more rows if needed.