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EU Annex 11 Guide to Computer Validation Compliance for the Worldwide Health Agency GMP



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EU GMP Annex 11 Guide

to Computer Validation Compliance for the Worldwide Health Agency GMP

Annex 15 – Cleaning Validation (3)

New Text:	Impact
10.5 For all cleaning processes an assessment should be performed to determine the variable factors which influence cleaning effectiveness and performance, e.g. operators, the level of detail in procedures such as rinsing times etc. If variable factors have been identified, the worst case situations should be used as the basis for cleaning validation studies.	No change to inspection process

Annex 15 – Cleaning Validation (6)	Impact
10.5 The cleaning procedure should be performed at an appropriate number of times to ensure the level of cleanliness is achieved. The number of cleaning cycles should be determined based on the level of cleanliness required. The number of cleaning cycles should be determined based on the level of cleanliness required. The number of cleaning cycles should be determined based on the level of cleanliness required.	No change to inspection process
10.6 Cleaning validation should be performed at a minimum once per year. The frequency of cleaning validation should be determined based on the level of cleanliness required. The frequency of cleaning validation should be determined based on the level of cleanliness required. The frequency of cleaning validation should be determined based on the level of cleanliness required.	No change to inspection process
10.7 When manual cleaning of equipment is performed, it is essential that the effectiveness of the manual process should be confirmed in a written procedure.	No significant change to inspection process Manual cleaning verified.

Annex 15 – Process Validation – Traditional Approach (1)	Impact
3.20 The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control. The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control. The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control.	Transition to PQ approach No change to 3 batch approach (3.20)
3.21 Without justification in 3.20, it is generally considered acceptable that a minimum of three batches are used for validation. An appropriate number of samples should be taken from each batch. The number of samples taken should be determined based on the level of cleanliness required. The number of samples taken should be determined based on the level of cleanliness required. The number of samples taken should be determined based on the level of cleanliness required.	Transition to PQ approach No change to 3 batch approach (3.20)

Annex 15 – Process Validation – Traditional Approach (2)	Impact
3.22 The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control. The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control. The number of batches manufactured and the number of samples taken should be sufficient to ensure that the process is under control.	Transition to PQ approach No change to 3 batch approach (3.20)

Eu gmp annex list. Annex 16 of the eu-gmp guidelines. Eu gmp guide-annex 15 qualification and validation draft released. Eu gmp guide-annex 15 qualification and validation. Annex 15 to the eu/pic/s guide to gmp. Annex 15 of the eu gmp guidelines.

Volume 4 of "The rules governing medicinal products in the European Union" contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary use laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC respectively. Introduction (07/02/2011) Commission Directive 2003/94/EC, of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Replacement of Commission Directive 91/356/EEC of 13 June 1991 to cover good manufacturing practice of investigational medicinal products. Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC. Commission Delegated Regulation (EU) 2017/1569 (for linguistic versions, click here) of 23 May 2017 supplementing Regulation (EU) 536/2014 of the European Parliament and of the Council by specifying principles and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials) Commission Directive (EU) 2017/1572 (for linguistic versions, click here) of 15 September 2017 supplementing Directive 2001/83/EC of the European Parliament and of the Council as regards the principles and guidelines of good manufacturing practice for medicinal products for human use (applicable as from the date of entry into application of Regulation (EU) No 536/2014 on Clinical Trials) Part I - Basic Requirements for Medicinal Products Part II - Basic Requirements for Active Substances used as Starting Materials Part III - GMP related documents Annexes Glossary Part IV - GMP requirements for Advanced Therapy Medicinal Products Other documents related to GMP 02/04/2015 In February 2014 the draft for the revision of EU GMP Annex 15 was published (see the GMP-News from 11 February 2014 "Revision of the EU GMP Annex 15 for Qualification and Validation published"). Compared with the currently valid version the changes were significant in some parts (see also the GMP-News from 21 March 2014 "Detailed Analysis of Annex 15 Draft"). Now the draft was published as final document and will be valid as of 1 October 2015. What will change? Following you will find an overview about the changes. With 16 pages the document is much more comprehensive than the current version (11 pages). In the section "principles" it is stated that the new EU GMP Annex 15 may also be used as supplementary optional guidance for active substances without introduction of additional requirements to EudraLex, Volume 4, Part II. Life cycles build the centre of the new Annex 15, whether with regard to the product or to the process, whether with regard to equipment and the process validation itself. A special emphasis is on risk management which is mentioned in several sections in the guideline instead of being mentioned in one section only on risk assessment. The new Annex 15 now specifically excludes a retrospective validation. Validation Master Plan The content of the validation master plan (VMP) has been extended. Deviation management is also supposed to be described in the VMP in the future, just as well as the standards for the development of acceptance criteria and the organisational structure. Compared to the draft version the mention of an "ongoing validation strategy" has been deleted. The request for naming the resources has also been omitted compared to the draft. Qualification The possibility to combine qualification documents (e.g. IQ and OQ as IOQ) is explicitly mentioned. It is also foreseen to include manufacturer documents. Fortunately there is the possibility of conditional releases in the area of qualification. The final document contains a requirement to establish user requirements and/or functional specifications as a starting point of a qualification. The DQ is now the second step in a qualification. Additional new requirements are the Factory Acceptance Test (FAT) and the Site Acceptance Test (SAT). Especially for equipment with new or complex technology a FAT "may" be conducted. Compared to the draft this is a less strict requirement. In the draft document it was stated that a FAT "should" be conducted. If appropriate and assessed, tests and documentation reviews as part of the FAT can be taken over in other steps without repeating them in the IQ/OQ. This is a very helpful definition. With regard to the PQ it is now also explicitly mentioned that (in certain cases) it can be combined with the OQ or the process validation. In the draft it is stated that IQ, OQ and PQ "should" be conducted. The chapter "Requalification" is new. Unfortunately the sub-chapter on established (in-use) equipment qualification has been completely omitted. Process Validation The options with regard to process validation have been extended. The previous "traditional" approach is still mentioned as a possibility, though - also with the determination of 3 validation batches. For a 3 batch validation further data from following batches may be necessary according to an "ongoing process verification". The possibility of a "continuous process verification" as described in ICH Q8, and a hybrid approach as a mix of the before mentioned two approaches is new. This is a clear difference to the US FDA Process Validation Guidance where only one approach is mentioned. According to the final EU GMP Annex 15 a "bracketing" approach can be used with respect to the number of runs, strength, batch size, packaging sizes and types. This is already known from the US. As part of the "ongoing process verification" the product quality should be monitored during the product life cycle to show that the "state of control" is fulfilled and that trends are assessed. This is also known as "Continued Process Verification" from the US. The "ongoing process verification" should be based and reported according to a protocol or equivalent documents, latter is new compared to the draft. Completely omitted has been the subject of a (regular) revalidation. The chapters "Transport Verification", "Packaging Validation" and "Qualification of Utilities" as well as a separate chapter on "Validation of Analytical Methods" are new. Compared to the draft the new final document now addresses also the qualification of equipment for secondary packaging. Cleaning Validation The chapter Cleaning Validation comprises clear changes. The number of subitems is more than double now. Fortunately it is possible now to group equipment if this grouping is justified accordingly. The acceptance criterion "visibly clean" as single acceptance criterion is designated as not acceptable. Limits for the carryover of contaminations are supposed to be based on a toxicological evaluation. There is a reference to the EMA Guideline on Shared Facilities (see GMP-News from 21 November 2014 "Shared and Dedicated Facilities: EMA publishes final Guideline on Setting health based exposure limits (PDEs)"). The EMA Guideline on process validation would have been desirable. Please find the new EU GMP Annex 15 on the EU Commission Webpage Afin de vous proposer le meilleur service possible, ASP utilise des cookies. En continuant de naviguer sur le site, vous déclarez accepter leur utilisation. 7-Apr-2014 Validation and qualification form an important part of the quality system in the pharmaceutical sector and can be defined in different ways. Tim Sandie, Head of Microbiology, BPL, UK discusses some standard definitions from a Good Manufacturing Practice (GMP) perspective. There are subtle differences between the terms 'validation' and 'qualification'. Validation is establishing documented evidence to provide a high degree of assurance that a specific system, process or facility will consistently produce a product meeting its predetermined specifications and quality attributes. Qualification is a process of assurance that the specific system, premises or equipment is able to achieve the predetermined acceptance criteria to confirm the attributes of what it purports to do. Qualification is about documented evidence that a specific equipment, facility or system is fit/ready for intended use and validation is documenting that the way the equipment, facility or system is used will result in a system meeting its predetermined specifications and quality attributes. To put it simply, things are attributed - equipment, systems and so forth - and process and procedures (the way we use things) are validated. Examples of things that are qualified include HVAC, pharmaceutical grade water, compressed air lines and so on. Calibration is also a part of qualification. Qualification would also apply to the training of a laboratory technician to run an assay. Examples of validation include manufacturing processes, cleaning processes, or an analytical method. Formal validation and qualification are both requirements of GMP. Within Europe, the accepted regulatory approach is set out in Annex 15 of the EU GMP Guide. The European Commission has recently published a draft version of Annex 15.1 The consultation document is available on the Commission's website, where the draft takes the form of a concept paper. The draft is currently available for public comment and a final version is expected during 2014. This article discusses some of the main changes that are being proposed for the Annex. GMP Annex 15 Annex 15 of the EU GMP guide is concerned with the 'Qualification and Validation' of pharmaceutical facilities, addressing requirements for equipment, utilities and processes that are used for the manufacture of medicinal products. The broad requirement of Annex 15 is that a pharma manufacturer needs to identify what qualification and validation work is required; next, the manufacturer must prove that critical aspects of work are controlled; and finally, the key elements of qualification and validation need to be defined and documented. Arguably the most important addition to the draft Annex is the inclusion of a section relating to change control. Given that the Annex was last updated in 2001, the 2013-2014 revision process has, unsurprisingly, led to some significant changes. Arguably the most important addition to the draft Annex is the inclusion of a section relating to change control. Change control is an established part of GMP and with respect to this any planned changes to the facilities, equipment, utilities and processes that may affect the quality of the product should be formally documented. With change controls, as the draft guidance indicates, written procedures should be in place to describe the actions to be taken if a planned change is proposed. The change process must assess whether the change during the lifecycle of the equipment or utility could affect product quality or reproducibility. From this assessment, certain changes may trigger a re-validation exercise. An example would be an update to computer software. As part of the validation of an item of equipment or a utility, the performance needs to be assessed. In the past, and as indicated in the current version of the Annex, the equipment should be qualified with three batches of product (or three process runs). With the revised version there is no longer any mention of three batches. This has been replaced by the requirement that: 'The number of batches manufactured and the number of samples taken should be based on quality risk management principles...'. This implies that a risk assessment is required. Before a qualification document is issued, the draft guidance makes a recommendation that the period and extent of qualification should also reflect any seasonal variations and the intended use of the utility. Another aspect referred to is, again, risk assessment. The draft recommends that a risk assessment should be carried out for any utility where there may be direct contact with the product. This would include, for example, HVAC systems and barrier devices used for aseptic filling. Cleaning validation has received increasing attention from the GMP inspectors in recent inspections. Another area of interest will be cleaning validation, which has received increasing attention from the GMP inspectors in recent inspections. Cleaning validation is the activity of ensuring that residues are removed from equipment as part of the cleaning (and sometimes disinfection or sanitisation procedure). All residues are removed to predetermined levels to ensure the quality of the next product manufactured is not compromised by waste from the previous product and the quality of future products using the equipment, to prevent cross-contamination and as a GMP requirement. The validation process here involves 'soiling' and measuring any chemical and microbiological residues. For this, pharmaceutical manufacturers must have written general procedures on how cleaning processes will be validated. The procedures should dictate who is responsible for performing and approving the validation study, sampling methods, analytical methods, physical parameters, the acceptance criteria, and when revalidation will be required. The guidance addresses the sometimes thorny issue of re-validation. This causes some debate within the industry in relation to when to re-validate and, some-times, if re-validation is required at all. The revised guidance is unambiguous: facilities, utilities, systems, equipment should be evaluated at an appropriate frequency to confirm that they remain in a state of control. Other reasons for the revision are procedural. The changes here take into account updates to other sections of the EU GMP Guide, including Annex 1 'Computerised Systems' (which was published in January 2011). An important part of validation procedure is the Validation Master Plan. This overarching document sets out the requirements of a validation exercise. The Annex provides useful guidance on putting the plan together. Master Plan A Master Plan should contain the following elements: Validation policy The organisational structure for validation activities Summary of the facilities, systems, equipment, processes on site and the current validation status Template formats to be used for protocols and reports Planning and scheduling Change control and deviation management for validation Handling of acceptance criteria References to existing documents An assessment of the resources required The on-going validation strategy, including revalidation and/or requalification, where applicable Confirmation that the materials used for validation are of the required quality and suppliers are qualified to the appropriate level Other aspects of validation documentation remain unaltered (including the standard Installation, Operational and Performance Qualification approaches). There are, however, some additions that bring the Annex in-line with other validation approaches. For this, the URS (User Requirement Specification) has been added to the section on Qualification for Facilities and Equipment, as has the Factory Acceptance Testing (FAT)/Site Acceptance Testing (SAT). The best documentation practices outlined in the Annex emphasise that the responsibility of performing validation must be clearly identified; that validation is conducted in accordance with predefined, approved validation protocols; and that recorded results and conclusions are presented in written validation reports. From the results of validation activities, Standard Operating Procedures (SOPs) should be generated. The final part of the Annex contains a revised and expanded glossary. Best practice In conclusion, the changes outlined in Annex 15 draw together examples of industry best practice under the GMP umbrella. Overall the draft Annex is an improvement upon the current version. The only criticism is that some parts remain open to interpretation (such as the scale of the activities required for re-validation) and with other aspects of the GMP guide there are no case studies. The inclusion of examples of best practice would have helped those tasked with assessing new equipment and utilities. The final version of the Annex is scheduled to be published in quarter four of 2014. References 1. 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 15: Qualification and Validation. See 2. EudraLex. The Rules Governing Medicinal Products in the European Community (Directive 2003/94/EC), Volume 4, Annex 15, published by the European Commission, Brussels, Belgium, 2001 Companies

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