EU QP：EU GMP Annex 1 CCS FQAs 2020

Q1 Can you explain a little bit more of negative pressure isolators?
A1 Negative pressure isolators should be avoided. However, especially when working with CMR-Substances this might not be possible.

Q2 Chapter 6: hydraulic systems: could you please give an example?
A2 6.21 Major items of equipment associated with hydraulic, heating and cooling systems, e.g. such as those associated with Blow-Fill-Seal equipment should, where possible, be located outside the filling room. Where they are located inside the filling room there should be appropriate controls to contain any spillage and/or cross contamination associated with the hydraulic system fluids. Hydraulic systems are often used for lifting and also are often found as pressure tools with Blow-Fill-Seal equipment.

Q3 Is there any plan to revise the "aseptic/sterile process" sections of the ATMP-Guideline and to align it with Annex 1?
A3 Currently not.

Q4 If decided, based on a rationale, not to perform PUPSIT (for simple buffer not likely to mask filter flaws), would it then be normal practice to submit the rationale to the authorities for approval before initiating the production?
A4 Most probably this has to be decided on a case by case basis. The document available is still a draft.

Q5 My colleagues from Manufacturing proposed the following cleaning approach of the floor in grade C and B when they are idle. Grade C: 1/week, Grade B: 1/month. Shouldn't Grade B be also1/week?
A5 Grade B cleaning should certainly be more frequent than Grade C. However when idle things are different. I suggest a decision based on principles of QRM is what you should do in first instance and then implement a plan.

Q6 Should CCIT performed on every batch?
A6 In general yes. Samples should be taken and checked for container closure integrity (CCI) using validated methods. The frequency of testing should be based on the knowledge and experience of the container closure system being used. A scientifically valid sampling plan should be utilized. The sample size should be based on information such as supplier approval, packaging component specifications and process knowledge. Remember: visual inspection alone is not considered as an acceptable integrity test method.

Q7 Should the MAH QP have access to the record mentioned (sterilization record), even though the manufacturing of the sterile product is outsourced to a CMO where the CMO QP is certifying the batch for partial manufacturing?
A7 Of course Annex 1 won't be in contradiction to Annex 16.

Q8 Is vial and stopper combination considered as "closed by fusion"?
A8 The following examples are given for closed by fusion:
8.21 […]e.g. Blow-fill-seal (BFS),Form-Fill-Seal (FFS), Small and Large Volume Parenteral (SVP & LVP) bags, glass or plastic ampoules […] vial and stopper combination is NOT considered as closed by fusion.

Q9 Will be CCS a formal auditable document?
A9 As the document(s) are requested by the current draft, CCS is considered as a formal auditable /

inspectable document.

Q10 Are there any real changes made to the requirements in Annex 1 or is it more clarification and expansion of already stated requirements?
A10 Both.

Q11 Regarding PUPSIT, most of the pharmaceutical Companies are not implementing it because it could induce additional risk for the product. Is it acceptable to justify it on a position paper? What's your though?
A11 Most probably this has to be decided on a case by case basis. The document available is still a draft.

Q12 Will the new version of Annex 1 also contain details about VHP sterilization?
A12 VHP sterilization is mentioned as an example in4.39 and 10.8.

Q13 What are your thoughts on oral vaccines manufactured as sterile products following Annex 1? Any waiver from Annex 1 could be acceptable? (e.g. no visual inspection, no endotoxin testing, any other...?)
A13 2.2 Processes, equipment, facilities and manufacturing activities should be managed in accordance with QRM principles to provide a proactive means of identifying, scientifically evaluating and controlling potential risks to quality. Where alternative approaches are used, these should be supported by appropriate rationales and risk assessment and should meet the intent of this Annex.

Q14 What do you propose to use as a documented QP evaluation of the impact of changes of the new annex, a gap assessment signed by the QP in charge? Or is a global update of the QMS sufficient?
A14 Both of these approaches are good. I would add that a top level Change Control be opened to manage the various strands of activity and that it get closed when the strands are closed, also ensure you put a time limit on completion dates for the strands! Do not let the strands of activity drag on indefinitely. Timeliness is always key.

Q15 When you are a non-sterile manufacturer but using the principles of Annex 1, would you advise documenting the elements utilised in a position paper or inherently documented into QMS SOPs?
A15 Both seems to make sense.

Q16 In a MA it is written, "filling has to be under Annex 1 class A conditions" However it isn't clear, if missing those should be handled as a deviation to the process or OOS related to the product (thus releasing the batch under an OOS), what do you think?
A16 In general compliance with the MA is a legal requirement. However, this is an equipment GMP matter not a release specification matter. I suggest a deviation is appropriate.

Q17 Is Annex 1 applicable to QC testing labs like sterility testing, micro lab? What is the concept?
A17 Annex 1 concepts should be applied to sterility testing arrangements. It makes sense that the testing arrangements in terms of Air Quality are at least as good if not better than the manufacturing arrangements, otherwise we cannot argue that the test is more reliable than the manufacturing. I suggest Annex 1 is not applicable to other micro related tests such as TVC counting, MLT etc.

Reference: 歐盟 QP 協會關於 EU GMP 附錄 1《無菌產品生產》的問答！(qq.com)