The revision of EU GMP Annex 1

32nd NKRV Workshop

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Nijmegen

The revision of EU GMP Annex 1

- The new Annex 1 will come into force on 25 August 2023
- Annex 1 has expanded from 16 to 58 pages!
- Annex 1 includes 11 chapters and over 500 paragraphs
- Includes new requirements as well as much more detail related to many of the requirements presented in the previous version
- Contains a strong focus on risk management - the term ‘Risk assessment’ is mentioned 20 times - and contamination control strategy

Annex 1 Gap Assessment

- At first, 40 GAPs between the previous and newly revised versions of Annex 1 were defined by us
- In the end, we defined 17 gaps (8 critical, 6 majors and 3 minors)

Contamination Control Strategy

2.3 A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. ….

Barrier technologies (e.g. isolators/hot-cells)

4.11 The transfer of materials, equipment, and components into the grade A or B areas should be carried out via a unidirectional process. …. If this is not possible, time-based separation of movement (incoming/exiting material) by procedure should be considered and controls applied to avoid potential contamination of incoming items.

Note: Establishing a unidirectional process for material transfer is straightforward when constructing new sites / hot-cells, but its implementation can pose challenges in existing sites.

Barrier technologies (e.g. isolators/hot-cells)

4.21 ….

i. Isolators:

a. …. Generally, glove integrity testing should be performed at a minimum frequency of the beginning and end of each batch or campaign. …. For manual aseptic processing activities where single unit or small batch sizes are produced, the frequency of integrity verification may be based on other criteria, such as the beginning and end of each manufacturing session.

Note: At our site, the glove integrity testing will become part of the weekly cleaning of our isolators and a visual inspection will be performed at the beginning and end of each batch.

Barrier technologies (e.g. isolators/hot-cells)

4.22 ….

i. For isolators

The bio-decontamination process of the interior should be automated, validated and controlled within defined cycle parameters and should include a sporicidal agent in a suitable form (e.g. gaseous or vaporized form). ….

Note: This is difficult to implement in an existing hot-cell.

Cleanroom and clean air equipment qualification

4.26 … initial classification should be performed during simulated operations and reclassification performed during simulated operations or during aseptic process simulation (APS).

4.29 Cleanroom classification should be carried out in the “at rest” and “in operation” states.

Aseptic preparation and processing

8.87 The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation prior to use.

8.89 The integrity of non-critical air or gas vent filters should be confirmed and recorded at appropriate intervals. …

Note: At present, we are in the process of formulating a justification to support the claim that PUPSIT does not provide any additional benefits to the safety of our products.

Quality control

10.3 The bioburden assay should be performed on each batch for both aseptically filled product and terminally sterilised products and the results considered as part of the final batch review. …

The proof of the pudding is in the eating.