TCD Workshop Qualified Person Workshop

DS and Sterile DP Manufacturing – Hot Topics

Susan Neenan, Stan O'Neill, Vincent O'Shaughnessy

What Topics Would you Like to Discuss?

Survey Conducted on Topics for a joint Drug Substance and Sterile DP Manufacturing Workshop/Discussion

- Several Topics That 'You' Highlighted…

Common Drug Substance and Drug Product Themes;

- Deviation Management and Annex 16
- Contamination Control Strategy – (Sterile and Low Bioburden processes)
- QP role in review/approval of batch records

Sterile Drug Product Topics

- What is emerging, 'Hot' or 'new' in the industry…… Open Door Assembly – Isolators (an evolving area of focus)?
- Aseptic Process Simulation Failures
- Visual Inspection and handling of defects

Drug Substance

- Application of Annex 1 including area classification (e.g. CNC) and challenges in inspections/audit findings

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Common Topics

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1. Deviation Management and Annex 16

Click to Return to Topic List

- How do QP's manage repeat events and recurrences
- How should a QP manage deviations without normalisation of risk?
- How should a QP manage deviations without normalisation of risk?
- What level of justification/documentation is required?
- How do QPs maintain independence?
- Navigating Challenging Deviations?
- Handling late-discovered deviations post-certification.

2. Contamination Control Strategy – (Sterile and Low Bioburden processes)

Click to Return to Topic List

- What should a “living CCS” practically look like?
- How are low bioburden DS facilities applying Annex 1 principles?
- How should CCS be linked to QRM?
  - Open vs closed processing — where is the regulatory expectation shifting?
- DS room classifications/Environmental Monitoring (Dispensing of final DS into final DS container) - Area Classification /Environmental monitoring .

Click to Return to Topic List

QP role in review of batch records?

- What constitutes sufficient QP oversight?
- Should QPs review every deviation and every EM excursion?
- Expectations for review of electronic batch records.
- Balancing operational efficiency versus detailed batch scrutiny.
- How much reliance can be placed on QA systems?
- What are expectations regarding QP knowledge of manufacturing processes?
- Management of contract manufacturing oversight .

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Sterile DP Topics

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Click to Return to Topic List

Open Door Assembly (Isolators – an evolving area of focus…)

…A move beyond risk-based layered control philosophies towards a process design that best preserves sterile state and minimises reliance on VPHP

1. Minimise reliance on VPHP as a post-exposure control, with greater emphasis on protecting sterilized parts during handling and assembly to reduce dependence on bio-decontamination for sterility assurance.
2. Demonstrate proactive sterility preservation — What feasible measures in design, technique, and control are applied to 'best' maintain the sterile state, rather than depending on VPHP to recover it after exposure.
3. Industry implications - Reassess and, where necessary, redesign aseptic controls and contamination control strategies with clear expectation for sterility preservation over post-exposure remediation.

Click to Return to Topic List

Open Door Assembly (Isolators – an evolving area of focus…)

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1. Minimise reliance on VPHP as a post-exposure control, with greater emphasis on protecting sterilized parts during handling and assembly to reduce dependence on bio-decontamination for sterility assurance.
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Click to Return to Topic List

Open Door Assembly (Isolators – an evolving area of focus…)

Some implications….which are perhaps not new?

- Sterilisation and handling of indirect product contact parts (stopper bowls, tracks, needle holders/clips etc.) - how to transfer during open-door assembly
- Strict aseptic technique to protect exposed product-contact (direct or indirect) surfaces during both pre-VHP and post-VHP operations for an isolator filling line
- Doctor & Nurse Concept to facilitate transition of materials, use of transition zone/proximity to Isolator to 'best preserve' sterile state
- Removal of Tyvek covers at last possible moment (varying interpretations).
- Not breaching first pass air during assembly – avoidance of torso from entering the Isolator
- Use of "sanitized" Isolator gloves to contact sterile parts – to be avoided : sterile equipment only to be contacted with sterile tools
- Augmented gowning controls (sterile sleeves, goggles, hood, mask, frock) with EM & PM during ODA.
- Charging of Stoppers and use of RTP Ports: Cannot breach first pass air – so getting stricter on RTP port opening being "touchless/automatic
- Increasing expectation on smoke studies (neutral buoyant, frame-by-frame review to assess for any and all breaches of first past air and ensuring clear visualisation

Click to Return to Topic List

Aseptic Process Simulation

- What constitutes a “failed” media fill?
- How should contaminated units be interpreted?
- Repeat media fill expectations after failures.
- Linkage between APS failures and commercial batch impact.
- Simulation of worst-case interventions.
- Role of operator qualification versus process design.

Click to Return to Topic List

Visual Inspection

- Manual versus automated inspection — what is expected?
- Qualification and requalification of inspectors.
- Defect libraries and probabilistic inspection approaches.
- Management of intrinsic versus extrinsic particles.
- Trending recurring defect categories.
- How should reject rates be interpreted?
- Container closure and cosmetic defect acceptance criteria.
- Integration of AI/machine learning inspection systems.
- Data integrity in automated inspection systems.
- Greater focus on probabilistic inspection science.
  - Regulatory concern over manual inspection variability.
  - Trending particulate complaints and recalls.

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DS Topics

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Click to Return to Topic List

Application of Annex 1 including area classification (e.g. CNC) and challenges in inspections/audit findings

- How should firms justify CNC in low bioburden DS facilities?
- • What contamination data are needed to support classification decisions?
- Expectations for open processing in CNC environments.
- Relationship between CCS and area classification rationale.
- Can closed systems justify lower classifications?
- Environmental monitoring expectations in CNC areas.
- Managing personnel and material flows in mixed-classification facilities.
- Challenges applying sterile DP principles to biologics DS.
- Common inspector concerns and observations.
- How should firms prepare defensible scientific justifications?
- Debate regarding CNC interpretation?.
  - Increased scrutiny on “open processing” definitions.
  - Regulators expecting stronger scientific rationale.
  - Greater alignment between Annex 1 and biologics DS expectations.
  - Increased use of closed processing technologies.