Challenges in Sterile product manufacturing

Discussion Group Session

8 topics covering challenges in sterile product manufacturing with risk based GMP
1. **Challenges around Moist heat sterilisation considering**: Understanding the basics, Equilibration time, Bowie Dick test for porous loads, applying $F_0$ zero, air removal, leak tests.
   Alan Heavey – Sterilization solutions Ltd to introduce this topic.

2. **Grade A continuity and Grade A air supply** – the challenge of understanding regulatory expectations and applying as contamination control measures.
   Tim Eaton: Sterile manufacturing specialist or Suzanne Nutter: sterile product manufacturing manager from Astra Zeneca will introduce this topic.

3. **Maintaining Sterility Assurance in Aseptic manufacturing through supply of pre-sterilised consumables and raw materials**.
   John Harries Steris Applied Sterilization Technologies Quality Director EMEA will introduce this topic.

4. **Barrier Separation Technology (Isolators and RABS) Glove leak integrity**: visual and physical testing expectations and risks from Barrier glove holes. Dr Stefan Merkle Senior Technical Operations Director Janssen Parenterals Belgium will introduce this topic.
5. Risk based and holistic environmental process monitoring – the challenge of risk assessments, setting sample locations, defining holistic EM programs and trending of data.
Ian Symonds; GSK Head, Aseptic strategy and intelligence, Pharma Ops, Global Functions and Benoit Ramond Head of Microbiology Sanofi will introduce this topic.

6. Incubation regimes for Environmental monitoring samples – the challenge of selecting a regime to deliver best chance of microflora detection/recovery.
Roland Guinet: Ex-Affsaps GMP Inspector GDMP consultant RGMP will present this topic explaining results from research supported by A3P; “Four incubation programs were used by 4 manufacturing pharmaceutical sites at 30 different locations each in grade C, D or CNC”.

7. Gowning and use of ‘Goggles’ in aseptic manufacturing – there is limited guidance in GMP, what is best practice?
Dr Tim Sandle, Head of Microbiology, Blood Products Ltd - BPL will introduce this topic.

8. Transfer of pre-sterilised product containers into Filling lines using Barrier technology the challenge implementing developing technologies.
Thorsten Hafner: Business development manager of Groninger Gmbh will present this topic
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<tr>
<td>1</td>
<td>Andrew Hopkins</td>
<td>MHRA</td>
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<td>Ian Symonds</td>
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<td>Eric Dewhurst</td>
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<td>Mike Davies</td>
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<td>Una Hearty</td>
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<td>Stefan Merkle</td>
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<td>Kay O-Hagan</td>
<td>Hospira UK/ Pfizer</td>
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<td>Tim Eaton</td>
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<td>9</td>
<td>Alan Heavey</td>
<td>UK Consultant</td>
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<td>10</td>
<td>Benoit Ramond</td>
<td>Sanofi/ Global</td>
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<td>11</td>
<td>Di Morris</td>
<td>GSK Global / ex MHRA</td>
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<td>12</td>
<td>Suzanne Nutter</td>
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<td>13</td>
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<td>Steris/ Synergy Health</td>
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<td>15</td>
<td>Thorsten Hafer</td>
<td>Groninger Germany</td>
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<td>16</td>
<td>Tim Sizer</td>
<td>HNS Regional QA Pharmacist</td>
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<td>17</td>
<td>Mark Oldcorne</td>
<td>All of Wales QA Pharmacist</td>
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Discussion moderator: James Drinkwater PHSS
If the basics of steam sterilization are not adequately understood – companies could ‘unknowingly’ be operating out of control....
We achieved 121°C, 20 min - all is well....
Meaningful methodology and monitoring

- Compliant Equilibration time - false confidence?

- Alternative Bowie & Dick (B&D) test - false positive?

- Risk Assessment (What number shall we chose?)
PHSS Conference
Challenges in Sterile Product Manufacture
Grade A continuity and Grade A air Supply
June 9th 2016, Cheshire, UK

Tim Eaton, AstraZeneca, UK Operations

June 2016
OPEN WORKSTATION TRANSFERS

Maintaining (EU) Grade A continuity within Grade B Background

Regulatory observations

• ‘Protective covering includes wrapping equipment/components in a single layer provided by autoclave bagging material……. There is no second layer to be removed in Grade B areas prior to entering the Grade A RABS’.

• ‘Autoclaved items (wrapped in autoclave bags) are openly transported and held on a cart in Grade B area while being used to set up filling equipment’

• ‘Receipt and storage of sterilized equipment/components/closures into the Class 100 area is described in SOP ………. The procedure includes passing exposed items (in autoclave bags) through Grade B for storage in Grade A without any secondary barrier’
OPEN WORKSTATION TRANSFERS

Considerations

- Is transfer/storage of equipment/components in/through a Grade B area no longer appropriate
- Many established facilities may (satisfactorily) utilise this process

Options

- Equipment/components sterilised in two wrappings
  - retained in the two wrappings following entry and storage in Grade B areas of the APA
  - outer wrapping removed in Grade B area prior to entering into Grade A zone

- Equipment/components sterilised in single wrapping
  - retained in a Grade A airflow environment following entry into the APA
  - in a cart (that maintains environment status), transferred through the Grade B area
  - removed from cart into Grade A airflow environment, and into Grade A zone
GRADE A AIR SUPPLY

Air protection pods for door barrier intervention and transfers - “A Pod” (Auxiliary air down flow HEPA unit)

(Courtesy Franz Ziel GmbH)

(Courtesy Howorth Air Technology Ltd)
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Challenges in Sterile product manufacturing

Discussion Group Session
Topic 3
Maintaining Sterility Assurance in Aseptic manufacturing through supply of pre-sterilised consumables and raw materials.

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Maintaining Sterility Assurance in Aseptic manufacturing through supply of pre-sterilised consumables and raw materials.

John Harries, Quality Director, Europe
Two aspects to radiation validation

- Dosimetric (physical) validation
- Microbiological validation (Dose Establishment)

Both are the responsibility of the contract giver

- Dosimetric validation is mandatory
- Microbiological validation depends on the product / material irradiated and the application.

- Material used in the aseptic manufacture of steriles may not require microbiological validation or a reduced validation.
Bioburden

• The underlying principal of terminal sterilization is low and consistent bioburden.

• Consistent bioburden is arguably the most critical.

• Radiation is a very effective sterilization method so relatively high bioburden is not an issue.

• It is important to establish a bioburden specification
Bioburden Reduction or Sterilization?

- Depends on the product or application of the component.
- Sterilization to achieve SAL (10^{-6}) is mandatory for C.E marked healthcare products.
- Bioburden reduction may be acceptable for a component entering an aseptic manufacturing environment.
- Bioburden reduction would require a lower radiation dose so could help address material compatibility issues.
Challenges in Sterile product manufacturing

Discussion Topic 4.

Barrier systems: Isolators & RABS
Glove Integrity testing
Visual inspection and Physical testing

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Risks – Regulations – Requirements in Barrier Glove Integrity testing

• Regulatory expectations are risk based without clarity of integrity test requirements for Isolator and RABS Barrier gloves.

• Risks from Glove holes are becoming more defined as research continues. The Glove entry risk with momentary pressurisation is a risk that may be the highest risk of contamination transfer so needs managing in technique and SOPs.

• The limit of Glove hole detection by integrity test devices is 70-100 micron and visual inspection limitations are around 500 micron. What does this mean relative to contamination risk?
Risks from Glove Holes – What testing is required

Based on the Knowledge of Glove Hole risks in contamination transfer what Glove integrity testing should be considered for Isolators and RABS?

Glove Hole size 500 micron
Simulation of glove entry and pressure transition from 50pa to 500pa with stable jet stream at 500pa pressure before equilibration to Barrier pressure differential.

Glove Hole size 100 micron
Challenges in Sterile product manufacturing

Discussion Group Session

Topic 5

Holistic EM Process Monitoring

Benoit Ramond
Risk based and holistic environmental process monitoring:
The Environmental Monitoring (EM) programs should include the following:
The viable EM programs - Discussion:

- How: Methods? Sample types?
  - Air: Active Air Sampling? Passive Air Sampling?
  - Surfaces: Contact plates? Swabs?
- Locations
  - Define: What is a sample?
  - Where?
  - Justification - Risk assessment?
- Frequency?
The viable EM procedure should include the following:

- **When?**
  - Routine: In operation? At rest?
  - Beginning? Middle? End?
  - During the campaign? End of the campaign?
  - Set-up of the equipment/filling machine?
  - After a critical intervention?

- **Limits?**
  - Action limits = Table from EU/GMPs/Annex 1?
  - Alert limits? Percentile (95% or 99%)?

- **Trending system?**
  - Use of the Contamination Recovery Rate (CRR) from USP<1116>?

- **CAPA system?**
Risk based and holistic environmental process monitoring

Discussion session

Topic 5

Holistic EM Process Monitoring

Ian Symonds
Discussion Points

• Microbiological monitoring is not an absolute measure of contamination level but at best it is an indicator of potential change.

• Technological development and better understanding of good aseptic practice has reduced Grade A recoveries and to a lesser extent Grade B to a rare occurrence.

• This reduces the ability to accurately trend and thus see and measure change.

• Whilst we will always need to monitor Grade A & B should we focus on the interfaces between B/C and C/D and targeted areas where transfer of contamination might take place.
Tunnel

Wash Area

C/Room

Equipment Prep

Filling Machine

Autoclave

Pass Through

Air Extracts

C/Room

MAL

= Grade D

= Grade C

= Grade B

= Grade A

Air supply

= Grade A

= Grade C

= Grade D
Risk Profiling and Proactive Response

• A detailed evaluation of personnel and materials movement and handling
• Alert and Action limits in Grade D and C should be based upon process capability and not just the published compliance limits if the data generated is to be of use
• Organisms will be detected in D/C interface and to a lesser extent in C/B – That is good!
• This can indicate how good the aseptic transfer / disinfection processes are working
• Provide information regarding the source of contamination
Risk Profiling and Proactive Response

• Action can be taken to eliminate or minimise bioburden before it is detected in the Grade B or Grade A locations where batches could be put at risk.

• Monitoring locations should be determined using a risk evaluation approach to bring them to a meaningful few.

• Unlike positive recoveries in Grade A this data should not be linked to the batch release.

• CAPAs should focus on ways of working and facility design.

• Control in the lower Grade zone DOES improve critical C/B or C/A (isolator) interfaces.
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Discussion Group Session
Topic 6

EM Incubation regimes

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MULTICENTRE STUDY EM APS INCUBATION REGIMES

**Locations**: France, 4 manufacturing sites, 30 points in grade C, D or CNC area in operations, 4 samples at the same location

**Media** bioMérieux EM: settle plates, contact plates neutralizers
liquid: TSB, Thioglycolate exposed 4 hours

**4 Regimes** EM: 22.5°C 5 days (3 + 2), 32.5°C ds (2 + 3), 22.5°C 3 ds then 32.5°C 2 ds total 5 ds, 32.5°C 2 ds then 22.5°C 3 ds total 5 ds

**4 Regimes** APS: 22.5°C 14 days (7 + 7), 32.5°C 14 ds (7 + 7), 22.5°C 7 ds then 32.5°C 7 ds total 14 ds, 32.5°C 7 ds then 22.5°C 7 ds total 14 ds

**Identification** EM: C+, C-, B+, B-, *Bacillus*, yeast, mould
**Identification** APS: idem + strict anaerobes for THIO

**TOTAL/medium**: 30 locations X 4 regimes X 4 sites = 480
4 Media: TSA settle plates + TSA contact plates + TSB + Thioglycolate
INCUBATION REGIMES

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<th>Medium</th>
<th>SP</th>
<th>CP</th>
<th>TSB</th>
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<tr>
<td>THIO</td>
<td>97.7</td>
<td>65.4</td>
<td>19</td>
</tr>
<tr>
<td>% growth</td>
<td></td>
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<td>% human/UFC</td>
<td>95.8</td>
<td>97.2</td>
<td>95.9</td>
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Very few/none C-, B-, *Bacillus*, Yeast, moulds, anaerobes

Total UFC: sites dependent from 1 to 4
C+ and B+ non *Bacillus*: better growth at 32.5°C EM + APS
Moulds: 17 + 9 UFC: 0 at 32.5°C only, 23 at 22.5°C
*Bacillus*: no differences between the 4 regimes
EM: 4 regimes no statistical differences after 5 days
APS: TSB = THIO, sterility test OK, thermal shock C+ and B+

Strategy proposed: routine EM and APS could be justified at 32.5°C and for EM periodic verification at 22.5°C
Problem: There is limited guidance available

Key issues:

- Goggles
  - Should goggles be mandatory for aseptic processing?
  - What does fully enclosed mean?
  - How to address operator claims of discomfort e.g. ‘misting up’?
  - Should goggles always be sterilised? (as opposed to sanitised)
Gowning

Key issues:
- Microbiologists often not involved in selection.
- How long should gowns be worn for?
- Are sterile disposable gowns better than re-laundered gowns?
- How often should gowns be washed and irradiated?
- Should gowns ever be repaired?
- Are current tests for gowns suitable (e.g. Particle tests by manufacture; contact plates on exit)?
Challenges in Sterile product manufacturing

Discussion Topic 8.

Introducing alternative technology:
Development of Pre-sterilised container Tub transfer in Filling lines via No-Touch-Transfer NTT - De-Bagging technology
Requirements for alternative technology

• New product profiles and small batch filling require alternative technology than ebeam/ VHP for pre-sterilised container Tub transfer.

• Filling Machine manufacturers develop automated/ semi auto de-bagging systems to meet new requirements.

• Process established as a No-Touch-Transfer: NTT based on the outside of the Tubs start sterile and if not contaminated during the transfer process then no outer surface decon step is required.

Step 1. Load closed Bagged Tub into De-bagger zone.

Step 2. Cut bag end open with bag end remaining clamped and closed. De-bagging zone Open design RABS with Grade B background transfer zone during Tub transfers.

Step 3. Open bag (vacuum pads) and complete No (Tub) Touch Transfer (NTT) via pusher outside of Bag. Tub Aseptic connection protected by Grade A air supply from contamination during bag opening and transfer.
Defining the process and solution

No-Touch-Transfer NTT technology integrated into RABS and connected to Filling systems in Isolators or RABS.

Outer tub surfaces verified as Sterile. Assurance of sterility through supply chain implemented by tamper proof label/ tape. Contamination transfer studies completed to verify sterile tubs and filling environment are not contaminated during NTT transfer.

Supply Chain
- QC certify at Warehouse receipt.
- QA Certify Secure Box with Tamper proof Label
- Manufacture containers Double Bag + Acumex Box. ETO Sterilise.

Filling in RABS
- De-Bag 1 NTT
- Manual Wipe Disinfect in Transfer

Filling in Isolator
- De-Bag 1 NTT

RABS Grade A ISO 5
Grade B ISO 7 Cleanroom background

Cleanroom Grade C ISO8

Isolator Grade A ISO 5