Bio-contamination control
PHSS Technical Monograph No. 20

Gordon Farquharson, July 2016
The UK PHSS (Pharmaceutical and Health Care Sciences Society) prepared Monograph No. 20 in September 2014.

This presentation includes some abstracts from the monograph to explain the principles. Readers intending to consider or use the principles explained, should read the complete document to ensure a full understanding of the approach recommended.
Introduction – What & Why?
Published September 2014 - A huge industry team involved (39 - authors, editors and reviewers)

PHSS Committee members.

UK MHRA Senior Inspectors (now Rapporteur for the EU/PICs Annex 1 revision). Ex MHRA inspector. Irish HPRA executive inspector.

Industrial microbiologists and QA professionals from GSK, Bio-Products, Astra Zeneca, GE Healthcare.

Experts in rapid micro methods (RMMs).

A professional editor.
Contents overview

1. A 200 page guideline
2. Founded on risk-based thinking
3. Contamination control strategies strongly focused on the use of isolators, RABS, and associated bio-decontamination
Contents - Divided into 5 main sections

1.0 Introduction and scope: Bio-contamination related to controlled environments
2.0 Bio-contamination risk profiling and characterisation
3.0 Bio-contamination monitoring including Rapid Micro Methods (RMM)
4.0 Bio-contamination control principles and guidance
5.0 Bio-contamination deviation management

Glossary of terms
Some important limitations

- When considering gaseous sporicidal decontamination methods:
  - Only covers vaporised hydrogen peroxide.
  - Doesn’t mention Chlorine Dioxide, Ozone or Nitrogen Dioxide.
- RMMs
  - Good overview of methods.
  - Focus on speed and convenience.
  - Identifies the challenge of comparative performance and sensitivity with traditional methods.
  - For me, doesn’t really identify the benefit in terms of less invasive monitoring of the Grade A core in aseptic processing.
- Doesn’t deal with important issues of ‘Blow-fill-seal’.
- Doesn’t address effective automation, closed processes, disposable technology or product design for reliability.
Doesn’t cover closed systems, SIP, and single use disposables
Key principles in PHSS Monograph #20

- Focus is aseptic processing, not the T/S route to sterility.
- Recognises that traditional microbiological based techniques for EM, media fills, and the sterility test are fragile, quite insensitive & limited.
- Wants to try to move away from waiting for deviations in critical zones → looking for changes in the micro profile in surrounding areas to give early warning.
- Assess risks – to manage and harden the critical zone interfaces and transits.
- Minimise interventions into the process core.
Coins a new(ish) concept and principle (RPPR)

• Risk Profiling Proactive Response (RPPR). [A PHSS Initiative].
  • Risk Profiling = Holistic view of normal CFU levels, incidence rates, & flora by group.
  • Proactive Response = An action taken before a contamination event or excursion outside regulatory limits occurs. A sophisticated ALERT process.

• The fundamental principle is that bio-contamination tracks through a facility; area to area; from the less to more clean; transferred by air, personnel and material movements; ultimately leading to a contamination event in the aseptic core. This risk is diminished a) if you make the boundaries more resilient & b) if you look for early signs of deterioration.

• Investigations of deviation events is expensive & disruptive, & therefore put more effort into avoiding deviations. In the first place.
Interaction diagram

Tries to explain the linkages to help ensure a holistic approach.
An interesting diagram explains the concept

Figure 2 Control targets in contamination levels for interconnected controlled areas.

Total particulate levels >>>>>>>>

3520000 (0.5 μ) 29000 (5 μ) << In Operation >>>>>>>>>>>>>>>>>>>>>>>>>>>
3520000 (0.5 μ) 29000 (5 μ) 3520000 (0.5 μ) 20 (0.5 micron)

A
ISO5
<1 cfu
= 0 cfu

Eliminated or restricted operator access to critical zone.

Microbiological Contamination as colony forming units (cfu) per controlled zone

EU : D
(a) 100
(b) 50
(c) n/a
(d) 200 cfu

3 log

C : ISO8
(a) 50
(b) 25
(c) n/a
(d) 100 cfu

3 log

B : ISO 7
(a) 5
(b) 5
(c) 5
(d) 10 cfu

3/6 log

a) Settle plates max cfu.
b) Contact plates max cfu.
c) Glove prints max cfu.
d) Active air cfu / cubic metre.

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Reinforces the continuum of separation
Traditional open cleanroom solution
Next stage up = RABS

Cleanrooms with RABS Separation Barrier Systems operated at positive pressure to minimum EU Grade B / ISO7 background (in operation).
Positive pressure isolator
Note: Recommends isolator in Grade C, not D as per Annex 1
Negative pressure isolator

Unclassified Areas / zones / PCCA

EU Grade D : at Rest
EU Grade C
in operation

ISO8 : In Operation
ISO8 in operation

Isolator -ve
EU Grade A
ISO 5
in operation

EU Grade C
at Rest

ISO7 in operation

Cleanrooms with Isolator separation barriers operated at a negative pressure differential to minimum background EU Grade D / ISO 8
An interpretation of the BFS GMP Guidance
Large scale Aseptic – Containment Filling of Freeze dried Biological products
Figure 3.9 *Small scale filling with RABS barrier technology.*

**Grade B – ISO 7 Cleanroom + vH₂O₂ decontamination**

+++ Pa: Pressure regime

*Open Design RABS*

Closed Operation RABS + inherent & corrective interventions.

Pre-sterilised Containers > De-bag 1.

Pre-sterilised containers: Air-clean / alcohol disinfection transfer

Single use systems (Product bag, lines) Air-clean / alcohol disinfection transfer

EM plates in VHP barrier packaging - vH₂O₂ decontamination transfer

Exit decontamination of outside of filled vials (virus clearance less than 30°C)

UDF airflow protection at Air-overspill access interfaces

Sterilised parts:

- Stopper bowl
- Caps bowl
- Track-ways
- Barrier Gloves
- Waste on exit

Product from formulation

Change rooms + pa

++ pa

Pre-packaged Sterile parts

vH₂O₂ +

Air clean
Provides guidance on the concept of Grade A continuity

Figure 3.16 Schematic diagram showing cleanroom layout designed for Grade A continuity.

Note that for simplicity the material and personnel air-locks are not shown.
Post Sterilisation - Control of components and change parts

For equipment which cannot be sterilized in place (SIP), wherever possible equipment and materials should be sterilized through double ended sterilizers, which open directly into a Grade A zone.

Where sterilizers are not directly adjacent to the location where aseptic operations are performed, Grade A continuity should be maintained for the transfer of materials from the sterilizer to the place of storage or use.
Post Sterilisation - Control of components and change parts

It is possible to use “clean air” protected carts. Where autoclave and oven carts are withdrawn from the sterilizer chamber into a Grade B room, there should be localized unidirectional Grade A airflow protection at the chamber outlet so items may remain under these controlled conditions until the load has cooled.
Post Sterilisation - Control of components and change parts

Where Grade A protection cannot be provided for autoclaved materials and components, the items should be sterilized double wrapped in coverings that permit air removal/steam entry and condensate removal while maintaining the sterile integrity of the contents.

Items which are pre-sterilized by other methods such as Gamma irradiation or ethylene oxide should be protected with appropriate wrappings to maintain their sterile integrity while outside the Grade A environment.
Grade A Continuity – Objectives

To maintain the sterility of sterilised goods being transferred through a Grade B areas.
Minimise contamination on the outside of packaging that has the potential to be transferred to the sterile goods when opened.
Grade A Continuity – Clean air transport systems

Enhancing the protection afforded to sterilised items:

• Product components → stoppers
• Machine change parts
• Transport & handling equipment

Double/Triple wrapping with storage and movement in Grade B not acceptable any more?
Lots of examples of process configurations – this in an isolator

Figure 4.7 Showing the plan of a Grade A filling enclosure with associated activities listed.
Finally - Looking forwards

• Clearly anticipates new revised Annex 1:
  • Anticipates expectation that, for aseptic processing, improved separation between personnel and process core will be expected/required.
  • Sees gaseous bio-decontamination as the best solution (top of the bio-decontamination hierarchy).
    • Links this to benefits of closed RABS and Isolators.
  • Promotes Grade A continuity for handling sterilised materials in cleanrooms.
• I hope this summary was useful, and helps you decide if there is value for you in it related to your aseptic processing requirements.

• Very EU focused (significant inspector input).

• The main theme is prevention of deviations (by tracking any shift from ‘normal’ status), rather than managing deviations (CAPA, etc.).

• Lots of isolator, RABs, and associated bio-decontamination guidance.