Sterile Processing – Current Challenges in Annex 1

Ashley Isbel

National GMP & Validation Forum

Hosted by PharmOut

PharmOut

Interactive Session

PharmOut

Session Overview

- The Purpose of this Session
- Annex 1 2008 as a tool for industry in 2016
- Some Interesting Issues
- Summary of the session

PharmOut

The Purpose of this Session

PharmOut

What to take home

So we are getting a new Annex 1 – What are you hoping for, and is it *really* what you want?

- Change is necessary
- Should we hope for prescriptive rules or general principles?
- To what extent should (can?) we demand of regulators what they demand of manufacturers?
- Are we 'grown up'?

PharmOut

Annex 1 (2008) in 2016

Annex 1 2008 vs Industry 2016

Where do I start – so many issues with Annex 1

- Clarity of wording and interpretation – Clause 51 anyone?
- Some requirements arguably unscientific (PUPSIT, 5 microns)
- Apparent contradictions (34 vs 116)
- Apparent important missing words (isolator concession in Grade A definition)
- Grammatical mistakes
- And now inconsistencies with referenced standards (14644)

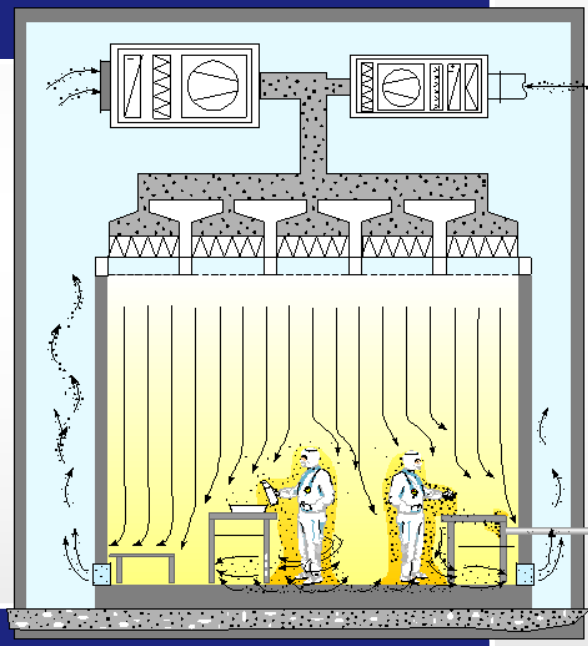
PharmOut

Some Interesting Issues

Airflow velocity measurements

Annex 1, 2008: *"Laminar air flow systems should provide a homogeneous air speed in a range of 0.36 – 0.54 m/s (guidance value)* ***at the working position*** *in open clean room applications."*

- Statement raises numerous questions:
  - Homogenous airspeed - What does it mean?
  - Is the speed range the average, or must all values comply?
  - Why state "guidance value"?
  - What is the working position?
  - If uni-directional airflow is demonstrated, why does the speed matter?



And why is this requirement fundamentally different from the FDA requirement? (0.45m/s ± 20% 6 inches from the filter face)

PharmOut

HEPA Filters, Testing & Patching

Annex 1, 2008: " … " There is no reference to HEPA filters in Annex 1!

Clean area air should pass through *"filters of an appropriate efficiency"*

- ISO 14644 parts 1 & 2 (2015) do not mention HEPAs
- ISO 14644 part 3 – provides HEPA leak test. Allows for patching only agreement between customer and supplier, and considering filter manufacturer instructions
- AS 1807.6 requires that patching information be recorded in report and provides some guidance on patch size, but its 16 years old!

What should we be doing??

PharmOut

HEPA Filters, Testing & Patching

Problems

- PIC/S ISO and AS provide no guidance on limitations of patching – size, area, patching materials?
- Filter manufacturers often discourage patching

There is help!

- BS EN 1822.4 & IEST RP-CC034.4 give detailed guidance on limitations of size/area
- Some manufacturers (eg. Camfill Farr) provide recommendations on patching material (hot melt silicone such as RTV 162, RTV 108, Dow 732) same as or similar to pleat separator

PharmOut

0.5 and 5.0 micron particles

Annex 1, 2008: Classification and monitoring required at both ≥0.5µm and ≥5.0µm

"≥5.0 µm particle concentration count takes on a particular significance as it is an important diagnostic tool for early detection of failure"

- On what basis is this statement made?
- ISO 14644 removed ≥5.0µm counting from the classification table for ISO 5 (Grade B at rest, basis for Grade A)
- Is it a problem to keep counting ≥5.0µm?

Again, we have a discrepancy between FDA and Annex 1 requirements. Do we need alignment on this issue?

PharmOut

0.5 and 5.0 micron particles

Some Thoughts

- Particle measurement equipment will measure multiple particle sizes simultaneously. ≥5 micron measurement requires no additional equipment
- Some people think it's important – maybe they're correct!
- Accuracy of sensors mean that ≥5 micron counts in Grade A are of questionable value, both in absolute terms (are they real particles?) and statistical (are trends meaningful?)
- Counter sampling rates mean that assessing ≥5 micron counts usually involves extrapolation over time

Incubation of EM plates and process simulation units

Annex 1, 2008: " … " no reference to incubation of EM or process simulation units

- 20-25°C followed by 30-35°C common practice
- Some reverse the order
- Some do different temperatures
- Some do one temperature
- USP historically supported two temperatures. Not specific anymore
- Different flora may have different optimal growing conditions (e.g. moulds typically prefer lower temperatures
- Mesophilic organisms are rarely growth inhibited between 20-35°C

Does your organisation have justification for the temperatures/times used?

Pre-Use Post-Sterilisation Integrity Testing of Product Filters

Annex 1, 2008: " *The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use …"*

- Also confirmed in PI007-6
- Why pre-use, post-sterilisation? Who says this is required?
  - Filter manufacturers?
  - Industry, based on knowledge of integrity failures?
  - Regulators, based on documented case studies?
- Cases in EU where major deficiencies assigned to manufacturers based on failure to PUPSIT.

Another example of failure to align with US FDA.

PharmOut

Pre-Use Post-Sterilisation Integrity Testing of Product Filters

Partial good news: New draft EMA guidance on sterilisation provides exception:

"The integrity of the sterilised filter should be verified before use but after its sterilisation unless specifically justified and validated"

ISO 13408-2 Revision also allows for risk-based decision on PUPSIT.

PharmOut

RABS & Isolators vs Traditional Open Lines

Annex 1, 2008: *"Restricted access barriers and isolators may be beneficial in assuring the required conditions and minimising direct human interventions into the capping operation."*

+ 5 clauses relating specifically to isolators

- Significant majority of Annex 1 (2008) is written for open lines
- Are new open lines acceptable?
- What are the implications for legacy lines if not?

Finally

Highlighted just 6 issues where industry and Annex 1 (2008) are not exactly aligned

PDA Points to Consider documents highlight 71 issues that the new Annex 1 should consider

- Several more that I would have liked to address today, but there isn't time

So what will the new Annex 1 say?

PharmOut

Finally

RABS & Isolators vs Traditional Open Lines

- Plenty of evidence that new Annex 1 will provide significantly increased guidance around barrier technology, and will advocate it more strongly
- Legacy traditional lines likely to continue to be acceptable if quality data is supportive
- Questions remain about new filling lines and manual processing

Airflow velocity measurements

- Expect significant clarification of unidirectional velocity requirements. Likely to be greater alignment with US FDA

HEPA Filters, Testing & Patching

- No indication if guidance on this will be introduced, probably unlikely. Consider application of good practice in any case

PharmOut

Finally

0.5 and 5.0 micron particles

- Indications are that *classification* will be in accordance with ISO 14644 requirements, so 5 micron will not be required at least for Grade B at-rest/Grade A
- But, likely that 5 micron will be required for continuous *monitoring*
- Hope that 5 micron may be used as indicative trending tool rather than limit based requirement

Incubation regimes

- No indication that incubation regimes will be subject of new Annex 1. If they are, likely to require evidence based justifications as described in updated USP 1116

PUPSIT

- Hope that a clause at least as flexible as that in EU sterilisation guidance may be included

PharmOut

What to take home

So we are getting a new Annex 1 – What are you hoping for, and is it *really* what you want?

- Change is necessary
- Should we hope for prescriptive rules or general principles?
- To what extent should (can?) we demand of regulators what they demand of manufacturers?
- Are we 'grown up'?

PharmOut