Interpreting the requirements of Annex 1 to achieve contamination control with cleaning and disinfection

Matt Cokely

Global Technical Consultant Regional Leader (APAC)

Ecolab Life Sciences

2023 Annex 1 Workshop Series (Singapore)

Agenda

- Annex 1 - How much changed and were there any final surprises for Cleaning and Disinfection?
- What was the impact for:
  - Cleaning and Disinfection
  - In-house preparation of cleaning/disinfection solutions
  - Residue management and Validation
  - Rotation
  - Material Transfer
- Summary/Questions

How much changed?

Document Attributes	2008 version	Feb 2020 (v.12) DRAFT revision	Aug 2022 LIVE Annex
Annex pages	16	52	58
Clauses	127	291	293*

- As we know, the deadline for complying with revised Annex 1 is 25 August 2023 (except for point 8.123 related to Lyophilizer sterilisation and barrier technology - postponed until 25 August 2024)
- Draft versions of Annex 1 were a good indication of where end users needed to assess (and in some instances change) their cleaning and disinfection strategies

Cleaning

Annex 1 (August 2022)

"4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed…. Cleaning programmes should effectively remove disinfectant residues."

Cleaning

Annex 1 (August 2022)

5 Equipment

"5.4 The cleaning process should be validated to be able to:

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.

ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection."

Cleaning

What the change is telling us….

- Surfaces to be disinfected must be clean
- Disinfectants may be chemically inactivated by the presence of soiling
- Need to avoid build-up of residues
- Residues or soiling could present a physical barrier preventing the disinfectants reaching the microbial cells
- Potential compatibility issues with different disinfectant products

Cleaning

What the change is telling us….

- Soil may result in poor penetration of Hydrogen Peroxide Vapour
- Risk based approach for cleaning frequency (dependant on manufacturing process and/or disinfectants used)
- Cleaning typical with water, detergent or 70/30 alcohol
- Detergents require rinsing prior to disinfection - adds additional steps
- Cleaning/disinfection should not interfere with manufacturing process or products

PIC/s Guide to GMP for Medicinal Products (PE 009-16 (Part I) Feb 2022)

"5.21 vii Design of cleaning processes for premises and equipment such that the cleaning processes in themselves do not present a cross-contamination risk; "

Disinfection

Annex 1 (August 2022)

"4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme…. More than one type of disinfecting agent should be employed ***to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent****.."*

"4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of disinfectants in the specific manner in which they are used and on the type of surface material, or representative material if justified, and should support the in-use expiry periods of prepared solutions."

Disinfection

What the change is telling us….

- Utilise a sporicide where risk appropriate/rotational requirements
- Regulatory requirement that *"The disinfection process should be validated"* Validation studies should be performed by customers – in the way they are used, on the materials they are used on
- Training/validation – reputable suppliers can advise on methods/conditions for validation: contact time, surfaces, organisms etc.

Disinfection

What the change is telling us….

- Regulatory requirements (PIC/S, Annex 1) specifies that in-use expiry periods (‘hold times’) should be validated by customers
- Ensure that the efficacy is effective throughout use and formulation stable
- Reliant on controlled storage conditions and operator preparation
- This links to the importance of training

In-house preparation of solutions

Annex 1 (August 2022)

"4.35 Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. ***Disinfectants used in grade C and D may also be required to be sterile where determined in the CCS****. Where the disinfectants and detergents are diluted/prepared by the sterile product manufacturer, this should be done in a manner to prevent contamination and they should be monitored for microbial contamination. Dilutions should be kept in previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period.*

If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted ***subject to successful completion of the appropriate vendor qualification****."*

In-house preparation of solutions

What the change is telling us….

- Validation of all the different variables and process need to considered
- WFI testing
- Filter suitability/compatibility
- In use expiry (‘hold times’) – Chemical and Microbiological?
- Bioburden studies

In-house preparation of solutions

What the change is telling us….

- May require sterile WFI and sterile containers
- Validation of the integrity testing of filters
- All has time and cost implications (consider ‘total cost’ of preparation)
- Disinfectants used in Grade C and D may also be required to be sterile depending on the risk (CCS)
- Need for vendor qualification acknowledged

Residues

Annex 1 (August 2022)

"4.33 The disinfection of cleanrooms is particularly important. They should be cleaned and disinfected thoroughly in accordance with a written programme. For disinfection to be effective, prior cleaning to remove surface contamination should be performed. Cleaning programmes should effectively remove disinfectant residues.."

"5.4 The cleaning process should be validated to be able to:

i. Remove any residue or debris that would detrimentally impact the effectiveness of the disinfecting agent used.
ii. Minimize chemical, microbial and particulate contamination of the product during the process and prior to disinfection."

Residues

What the change is telling us….

- Build up of visible residues demonstrates to regulators that cleaning & disinfection processes are not in control
- Potential for interaction/inactivation between different chemistries
- Residue (or debris) could detrimentally impact the effectiveness of the disinfecting agent used
- Residues are potential chemical and particulate contaminants

Residues

What the change is telling us….

- Could impact on the product being manufactured during the process and prior to disinfection
- Residues could potentially affect environmental monitoring (neutralizers in media unable to work)
- Residues left for prolonged periods may cause corrosion of expensive equipment
- H&S concerns

Validation

Annex 1 (August 2022)

4 Premises

Disinfection

"4.34 The disinfection process should be validated. Validation studies should demonstrate the suitability and effectiveness of ***disinfectants in the specific manner in which they are used and on the type of surface material, or representative material*** *if justified, and should support the in-use expiry periods of prepared solutions"*

"4.35…Dilutions should be kept in previously cleaned containers (and sterilized where applicable) and should only be stored for the defined period. If the disinfectants and detergents are supplied "ready-made" then results from certificates of analysis or conformance can be accepted subject to successful completion of the appropriate vendor qualification."

Validation

Annex 1 (August 2022)

4 Premises
Disinfection

"4.36 Where fumigation or vapour disinfection (e.g. Vapour-phase Hydrogen Peroxide) of cleanrooms and associated surfaces are used, the effectiveness of any fumigation agent and dispersion system should be understood and validated"

Validation

Outside of Annex 1….

PIC/S PI 007-6 – Recommendation on the Validation of Aseptic Processes Jan 2011
"The effectiveness of disinfectants and the minimum contact time on different surfaces should be validated"

FDA Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – current GMP Sept 2004

"The suitability, efficacy, and limitations of disinfecting agents and procedures should be assessed. The effectiveness of these disinfectants and procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces."

USP 43 NF 38 <1072> Antiseptics and Disinfectants
"To demonstrate the efficacy of a disinfectant…it may be deemed necessary to conduct the following tests:
(1) use-dilution tests
(2) surface challenge tests
(3) a statistical comparison of the frequency of isolation and numbers of microorganisms isolated prior to and after the implementation of a new disinfectant"

Validation

What the change is telling us….

- Annex 1 (and other guidance) suggests need for in vitro (lab testing) and in situ testing (phase III trials)
- Studies should demonstrate the suitability and effectiveness of disinfectants *"in the specific manner in which they are used"*
- Suggests that modified test methods, Validex™ and methods incorporating mechanical action are acceptable and expected
- In-use expiry periods of prepared solutions is required
- Consider need to validate neutralisers in EM contact plates (Annex 15)

Rotation

Annex 1 (August 2022)

"4.33… More than one type of disinfecting agent should be employed to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi. Disinfection should include the periodic use of a sporicidal agent.

Monitoring should be undertaken regularly in order to assess the effectiveness of the disinfection programme and to detect changes in types of microbial flora (e.g. organisms resistant to the disinfection regime currently in use)."

Rotation

What the change is telling us….

- There is no industry standard for rotation
- Annex draft advises that a disinfection programme *“should include the periodic use of a sporicidal agent”*
- Sporicide use ‘as required’ (use of sporicide only when EM results are OOS) is reactive behaviour, and not recommended
- EM data should be used to justify the frequency – if EM is in control then the current frequency is likely to be appropriate

Rotation

What the change is telling us….

- Rotation should provide full spectrum of microbiocidal activity, without the need to continually use a sporicidal agent
- Annex v.12 describes using *“more than one type of disinfecting agent…..to ensure that where they have different modes of action, their combined usage is effective against bacteria and fungi”*
- Reference to ‘resistance’ still seems to imply observed changes to flora could be due to development of resistance

Material Transfer (Transfer Disinfection)

Annex 1 (August 2022)

"4.18 Isolators or RABS, which are different technologies, and the associated processes, should be designed to provide protection through separation of the grade A environment from the environment of the surrounding room.

The hazards introduced from entry or removal of items during processing should be minimized and supported by high capability transfer technologies or validated systems that robustly prevent contamination and are appropriate for the respective technology."

Material Transfer (Transfer Disinfection)

Annex 1 (August 2022)

4 Premises

"4.12 ii Material airlocks: used for materials and equipment transfer.

- *Only materials and equipment that have been included on an approved list and assessed during validation of the transfer process should be transferred into the grade A or grade B areas via an airlock or pass-through hatches. Equipment and materials (intended for use in the grade A area) should be protected when transiting through the grade B area. Any unapproved items that require transfer should be pre-approved as an exception. Appropriate risk assessment and mitigation measures should be applied and recorded as per the manufacturer's CCS and should include a specific disinfection and monitoring programme approved by quality assurance. "*

Material Transfer (Transfer Disinfection)

Annex 1 (August 2022)

4 Premises

"4.12 ii

- *Pass-through hatches should be designed to protect the higher-grade environment, for example by effective flushing with an active filtered air supply.*

- *The movement of material or equipment from lower grade or unclassified area to higher-grade clean areas should be subject to cleaning and disinfection commensurate with the risk and in line with the CCS."*

Material Transfer (Transfer Disinfection)

Outside of Annex 1….

PIC/S PI 007-6 – Recommendation on the Validation of Aseptic Processes Jan 2011
"Sporicidal agents should be used wherever possible but particularly for "spraying-in" components and equipment in aseptic areas."

MHRA Guidance for Specials Manufacturers 2015:
"Before transfer to the manufacturing room, a sanitisation step using a spray and wipe technique including a sporicidal agent designed to inactivate bacterial and fungal spores must be carried out."

Material Transfer (Transfer Disinfection)

What the change is telling us….

- Only approved materials and equipment should be transferred
- Processes based on understanding of risk to process
- Utilize a sporicide where risk appropriate (*"commensurate with the risk"*)
- Inspection findings trends show this is easy to get wrong

In Summary…

- Much of the final version of Annex 1 remained the same, or similar to previous drafts with regards cleaning and disinfection
- Some of the 'core' or key messages are:
  - Cleaning and control of residues
  - Consideration of the use of sterile products in Grades C/D based on QRM
  - Vendor qualification, potential benefits and reduced risk of RTU in Grades A/B
  - Validation of disinfectants "in the specific manner in which they are used" (including storage periods)
  - Closer control of Material Transfer processes
- Reputable manufacturers recommendations should remain in line with Annex 1 August 2022. Consult your suppliers!

Thank You

Any questions?