Annex 1 Manufacture of Sterile Products: Highlights from previous draft version

Discovering Endless Breakthrough Opportunities

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About ADRES

ADRES' team of consultants guide startups and established companies as they navigate complex medical regulatory environments. From novel medical devices to new biopharma creations and technologies, ADRES has the experience and relationships to help secure regulatory approval in the United States, Europe, Israel, and globally.

ADRES clients operate in multiple fields, in the pursuit of treatments for an array of medical conditions. They include vaccines, biologicals, cell therapies and ATMPs, botanical drugs, liposomes, and medical devices. Our clients are located around the globe, including Israel, USA, Europe, Brazil, India, and China.

Our European subsidiary ADRES EU B.V. is located in Amsterdam, The Netherlands. Holding SME status, ADRES EU includes other small companies, enabling access to a variety of regulatory benefits (e.g. considerably reduced fees when approaching a scientific advice meeting with the European Medicines Agency – EMA).

ADRES EU also serves as the European Representative during the conduct of clinical trials for pharmaceuticals and medical devices, as well as the European Representative for CE-marked medical devices.

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1 Annex GMP EU

The EU GMP Annex 1: Manufacture of Sterile Medicinal Products has undergone its first official update since 2008. The guideline has been completely rewritten, expanding from 16 to 58 pages, and requires a completely different approach.

The guideline had been updated in draft form multiple times. New updated drafts were published for comment several times, until the final revision was released last August.

The drafts represented better structure, considered new technologies, stated that quality risk management should be used, and introduced the concept of a living contamination control strategy document that should be continuously updated and improved to control potential risks to quality, and more.

Hereunder are the changes made from the last draft published in December 2020 to the 2022 final revision:

1. Addition of raw materials and packaging materials as a key area to consider, to control and test as to ensure the level of bioburden, endotoxin/pyrogen.
2. Addition of management engagement: effectiveness of the CCS should be a part of the periodic management review; senior management should effectively oversee the state of control throughout the facility and product lifecycle.
3. The following element to consider in the CCS was added: Validation of sterilization processes. Also, the frequency of RABS glove replacement should be defined within the CCS.
4. Emphasis the need in detailed investigation (before release of the batch) and root cause determination through the document.
5. Clarifies that Changes to the systems in place should be assessed for any impact on the CCS before and after implementation.

6. Particulate contamination was updated to ‘particle’ throughout the document.
7. Emphasis that sliding doors may be undesirable due to their design that should avoid recesses.
8. Airlocks- Annex makes it very clear that where the CCS indicates that the risk of contamination is high, separate change rooms for entering and leaving production areas should be used.
9. This revision makes clear separation between isolator and RABS requirements.
10. Requirement for background environment for open isolator was updated to a minimum of grade C and for closed isolator grade D.
11. Addition of key considerations to CCS of an isolator: the bio-decontamination program, the extent of automation, the impact of glove manipulations that may potentially compromise ‘first air’ protection of critical process points, the impact of potential loss of barrier/glove integrity, transfer mechanisms used and activities such as set-up or maintenance that may require the doors to be opened prior to the final bio-decontamination of the isolator.
12. Addition of instruction to visually inspect the RABS/isolator gloves associated with each use.
13. Clarification regarding RABS gloves- If exposed to the background environment during operation, disinfection using an approved methodology following each exposure should be completed.
14. Decontamination/disinfection was updated to Bio-decontamination (added also in glossary: -A process that eliminates viable bioburden via use of sporicidal chemical agents).
15. For cleanroom classification:
    a. Addition of instruction to consider 5µm particles measurements where limits are not specified.
    b. Limits for total particles equal to or greater 5 µm/m3 were updated (aligned with ISO 14644).

c. Addition of instruction to achieve the total particle limits 'at rest' also after line clearance/ cleaning activities.

d. The clean-up period (period between completion of operations/line clearance/cleaning activities and total particle sampling at 'at rest' state) was updated to be less than 20 minutes.

16. Validation studies of disinfection program should include effectiveness on the type of surface material (or representative material if justified).
17. The effectiveness of any fumigation agent and dispersion system should be understood and validated.
18. Bend radius of particles counter should be acc to the manufacturer's recommended specifications.
19. Water systems:

    a. Validation of the water system is required.

    b. Water flow rates should be established during qualification and routinely monitored.

    c. WFI should be produced by distillation or by a purification process that is equivalent to distillation.

    d. WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters- addition of instruction to controls that should be in place to prevent condensation formation on the filter (e.g., by heating).

    e. Addition of instruction to microbiological/endotoxin results verified to be within specification and approved before batches manufactured using water from the system are considered for release.

    f. Sampling program focus on all outlets and points of use, at a specified interval.

    g. Deleted the option to justify no use in continuous monitoring systems such as Total Organic Carbon (TOC) and conductivity.

20. Clarification that microbial testing is not mandatory for steam condensate.
21. Deleted the instruction that for both vacuum and cooling systems there should be periodic cleaning/disinfection.
22. Garments should be sterilized (the option for effectively decontaminated was removed).
23. Addition of instruction to wear sterilized, non-powdered, rubber or plastic gloves while donning the sterilized garments (grade A+B).
24. Addition of instruction: the particle shedding and the particle retention efficiencies of the garments should be assessed during the garment qualification.
25. Addition of consideration to wear facemask and additional gowning in grade C, D when performing activities considered to be a contamination risk as defined by the CCS.
26. Clarification re socks (outdoor gowning)- should not be brought into changing rooms leading directly to grade B/C areas.
27. Addition of instruction: the garment management processes should include a maximum number of laundry and sterilization cycles.
28. Expansion on the interventions design (to ensure that the risk of contamination of the environment, process and product is effectively minimized).
29. The Quality unit should authorize non-qualified interventions, and their impact should be assessed during batch disposition.
30. Interventions and stoppages should be recorded in the batch record (associated time, duration of the event, and operators involved).
31. Integrity testing for final containers closed by fusion- updated that for large vol. containers >100ml reduced sampling may be acceptable.
32. Grade A air supply- clarification that the background environment should meet at least grade D.

33. Addition of requirement to verify the purity of the indicator organism of the batch/lot should be verified for new batch/lot of BI.
34. The sealed packaging (for sterilization) of materials, equipment, components and ancillary items should be qualified for minimizing the risk of particulate, microbial, endotoxin/ pyrogen or chemical contamination, and for compatibility with the selected sterilization method.
35. Sterilization by heat- the system should have safeguards and/or redundancy in its control to detect a cycle not conforming.
36. Dry heat sterilization- Clarification that no additional requirement to demonstrate sterilization in cases when a thermal process is used as part of the depyrogenation process.
37. Sterile filtration:
    a. the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter should be included in the batch record, as well as other critical process parameters.
    b. The integrity test process should be validated.
    c. Clarification re Bioburden samples where a redundant filtration set-up is used - it should be taken prior to the first filter.
38. Form-Fill-Seal (FFS) section was broadly updated.
39. BFS:
    a. In operation monitoring of total particle for Blow-Fill-Seal equipment is not expected. Further expectation re viable monitoring provided (risk based, in operation for the full duration of critical processing).
    b. Added aspects to be considered in controls identified during qualification and critical process parameters.
40. Lyophilizer sterilization: The frequency should be determined based on the design and risks related to system contamination during use.
41. EM and process monitoring:
    a. added the following element as part of the environmental and process monitoring program: “Temperature, relative humidity and other specific characteristics”.

b. Clarification that more stringent action limits may be applied to viable and total particle monitoring based on data trending, the nature of the process or as determined within the CCS.

c. Terminology changed: non-viable particles to total particles.

d .Losing the term 'objectionable', instead: organisms recovered that may indicate a loss of control, deterioration in cleanliness or organisms that may be difficult to control such as spore-forming microorganisms and moulds.

e. Limits for total particles equal to or greater 5 µm/m3 were updated (aligned with ISO 14644).

f. Addition of instruction to achieve the total particle limits 'at rest' also after line clearance/ cleaning activities.

g. d.The clean-up period (period between completion of operations/line clearance/cleaning activities and total particle sampling at 'at rest' state) was updated to be less than 20 minutes.

h. Addition of instruction to monitor cleanroom and equipment surfaces for viable particle at the end of an operation.

i. Personnel sampling- Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.

j. Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit.

42. Aseptic process simulation:

a. clarification that it should not be used to justify practices that pose unnecessary contamination risks.

b. Update that for manual operations (e.g., aseptic compounding or filling) each type of container, container closure and equipment should be revalidated with one APS approximately every 6 months for each operator.

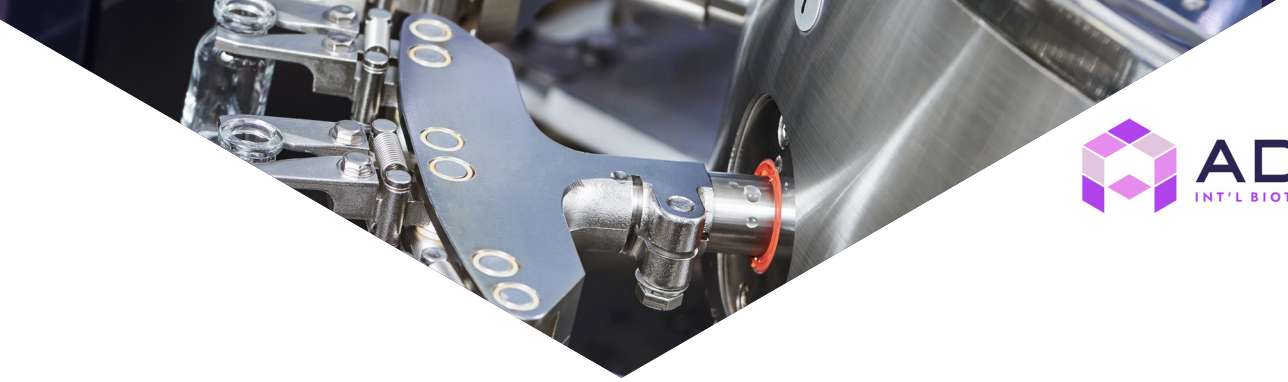
c. Discarding units during APS and not incubating is allowed only if occurring during routine fill and production SOPs clearly specify that units must be removed under the same circumstances (i.e., type of intervention; line location; specific number of units removed). In no case should more units be removed during a media fill intervention than would be cleared during a production run. Anyway, justification for filled and non-incubated units should be included in the documentation

d. Added instruction to incubate separately the units that are discarded during routine production to fully understand the process and assess contamination risks during aseptic setup or mandatory line clearances. These units would not necessarily be included in the acceptance criteria for the APS.

e. removed the need to inspect the incubated APS units in conditions similar to those for visual inspection.

f. Added the instruction: An APS run should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. An investigation should be documented in such cases

43. QC personnel should be trained and experienced with sterility assurance.
44. Added the instruction that specifications for raw materials, components and products should include requirements for particulate and endotoxin/pyrogen limits.
45. Clarify the samples to be taken during aseptic filling: during beginning and end (discarded the middle) and after critical interventions- considered based on risk.
46. Added the instruction to perform the GPT of the media used for EM and APS before use, using a scientifically justified and designated group of reference microorganisms and including suitably representative local isolates.
47. The definitions of active, passive, open and closed RABS were discarded.



The implementation is expected to take place both in existing and in new facilities (with no distinction). Facilities that are already compliant will most likely not experience any major impact or disruption but should expect minor adaptations to their processes.
Many of the changes are more stringent than in the previous versions. We are currently in the transition period, with the operation deadline coming into effect on 25 Aug 2023 (one year from the date of publication).

Whether you are a sterile manufacturer or not, take some time to create a plan of action. The implementation of some requirements is not straightforward and might take some time to comply with.
Reach out to ADRES for guidance in complying with the updated version of EU GMP Annex 1: Manufacture of Sterile Medicinal Products

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