



Wrapping and Sterilization of Product Contact Equipment for Compliance with Annex 1

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Agenda

- CCS Life Cycle
- Sterilization Preparation/Wrapping
- Autoclave Sterilization
- Sterile Parts Transport and Storage
- Line Assembly
- Implementation of CCS
- Conclusion (Q&A)



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Contamination Control Strategy (CCS)

A planned set of controls for microorganisms, endotoxin/pyrogen and particles, derived from current product and process understanding that assures process performance and product quality. The controls can include parameters and attributes related to active substance, excipient and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.













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Primary and secondary covers for product contact surfaces







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What is the Purpose of Sterilization Wrapping?

WHO Technical Report Series 961 – SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS Annex 6: WHO good manufacturing practices for sterile pharmaceutical products

6.5 The items to be sterilized, other than products in sealed containers, should be wrapped in a material that allows the removal of air and the penetration of steam but prevents recontamination after sterilization... All parts of the load should be in contact with water or saturated steam at the required temperature for the required time. Manufacturers of <u>aseptically</u> filled drug product need to protect product contact surfaces through sterilization, until time of use on the filling line.



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What is the Purpose of Sterilization Wrapping?

EU Annex 1, Section 8.48

Where materials, equipment, components and ancillary items are sterilised in sealed packaging or containers, the packaging should be qualified for minimizing the risk of particulate, microbial, endotoxin/pyrogen or chemical contamination, and for compatibility with the selected sterilisation method. The packaging sealing process should be validated. The validation should consider the integrity of the sterile protective barrier system, the maximum hold time before sterilisation and the maximum shelf life assigned to the sterilised items. The integrity of the sterile protective barrier system for each of the sterilised items should be checked prior to use.

Manufacturers of *aseptically filled* drug product need to *protect product contact surfaces* through sterilization, until time of use on the filling line.



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Autoclave Sterilization

2.1, 2.2: General requirements for manufacturing of sterile products – premises, design, verification, qualification, training, management, quality system

- 4.5: Requirements for equipment surfaces, cleanability
- 4.6: Requirements for minimizing accumulation of particles, impurities, contamination
- 4.7: Design to minimize creation of particles
- **4.10:** Requirements for controlling, monitoring and maintaining contamination control in all material transfer (airlocks, sterilizers)
- 4.11: Requirements and preferences for transfer of materials (in reference to sterilization)
- 5.1: Equipment design specification
- 5.2: Equipment monitoring requirements
- 5.3: Design & installation requirements for cleanroom & equipment utilities & technical areas
- 5.6: General requirements for qualification, monitoring and maintenance

6.1 – 6.6: Design, installation, qualification, operation, maintaining and monitoring of critical utilities (in reference to sterilization)

6.16, 6.17: Critical utility requirements specific to use of pure steam (in reference to steam sterilizers)





Product Contact Equipment Life Cycle Autoclave Sterilization

Autoclave Sterilization

8.34: Requirements and preferences for sterilization and types of processes used

8.35: Requirements and preferences for sterilizer locations, cycles and parameters

8.36: Requirements for validation of sterilization processes

8.37: Requirements for adoption of other sterilization modalities (in reference to e.g., low temperature sterilization by VHP[®])

8.38: Requirements for sterilizer load patterns

8.40: Requirements for routine monitoring of sterilizers in production use

- 8.41: Requirements for detecting a failed sterilization cycle
- 8.42, 8.43: Requirements for biological indicators

8.45: Requirements for sterilization cycle records

8.55 – 8.65: Requirements for various types of moist heat sterilization processes (vacuum cycles, pressure cycles, saturated steam, superheated water cycles – porous loads / hard goods, liquid loads) – design, performance verification, validation – air removal, leak rate testing, load and temperature mapping





Autoclave Sterilization

2.1 - 2.2: General requirements for manufacturing of sterile products – premises, design, verification,

qualification, training, management, quality system

- Appropriately designed facilities
- Conform to GMP requirements
- Quality risk management (QRM) principles followed
- Quality control, verification and management in place
- Trained personnel operating around the equipment





Autoclave Sterilization

8.35: Requirements and preferences for sterilizer locations, cycles and parameters

- 8.38: Requirements for sterilizer load patterns
- 8.40: Requirements for routine monitoring of sterilizers in production use
- 8.41: Requirements for detecting a failed sterilization cycle
- 8.45: Requirements for sterilization cycle records



- Design and cycles developed per scientific principles parameters defined, controlled and recorded
- Independent monitoring of critical cycle (chamber) variables pressure, temperature (see also EN 285)
- Validation of sterilizers and processes/cycles should be a part of the holistic view of the entire product process before and after not only the sterilizer
- Establish validated loading patterns
- Validation by biological indicators (BI), and to include also the sterilizer chamber surfaces, carts, etc.



Autoclave Sterilization

8.55 – 8.65: Requirements for various types of moist heat sterilization processes (vacuum cycles, pressure cycles, saturated

steam, superheated water cycles – porous loads / hard goods, liquid loads) – design, performance verification, validation

- Sterilized goods to be packaged appropriately
- Product dryness requirements/inspection
- Time/temperature/pressure to be recorded, parameter limits and tolerances specified
- Validation of fluid cycles should include temperature, time and/or $\rm F_0$
- Validation of porous cycles should include a calculation of equilibration time, exposure time, correlation of pressure and temperature and the minimum/maximum temperature range
- Requirement for periodical leak rate tests (e.g., weekly)
- Air removal system/test cycle
- Temperature mapping of superheated water processes



A portfolio of GMP steam sterilization cycle types for GMP manufacturing applications



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Autoclave Sterilization





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Autoclave Sterilization Validation

EU Annex 1, Section 8.36

All sterilisation processes should be validated. Validation studies should take into account the product composition, storage conditions and maximum time between the start of the preparation of a product or material to be sterilized and its sterilisation. Before any sterilisation process is adopted, its suitability for the product and equipment, and its efficacy in consistently achieving the desired sterilizing conditions in all parts of each type of load to be processed should be validated notably by physical measurements and where appropriate by Biological Indicators (BI). For effective sterilisation, the whole of the product, and surfaces of equipment and components should be subject to the required treatment and the process should be designed to ensure that this is achieved.

Product

- Composition
- Storage conditions
- Hold times

Sterilization method

- Suitability
- Efficacy

Validation

- Physical measurements
- Biological indicators
- All equipment surfaces



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Autoclave Sterilization Validation

EU Annex 1, Section 8.38, 8.39

Validated loading patterns should be established for all sterilisation processes and load patterns should be subject to periodic revalidation. Maximum and minimum loads should also be considered as part of the overall load validation strategy.

The validity of the sterilizing process should be reviewed and verified at scheduled intervals based on risk. Heat sterilization cycles should be revalidated with a minimum frequency of at least annually for load patterns that are considered worst case. Other load patterns should be validated at a frequency justified in the CCS.

Loading patterns

- Maximum
- Minimum

Revalidation Timing

- Periodic
- Risk-based frequency
- Minimum annually for worst-case loads



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Biological Indicators

EU Annex 1, Section 8.43

The reliability of BIs is important... Prior to use of a new batch/lot of BIs, the population, purity and identity of the indicator organism of the batch/lot should be verified. For other critical parameters, e.g. D-value, Z-value, the batch certificate provided by the qualified supplier can normally be used.



End-User Verifies

- Population
- Purity
- Organism identity

Manufacturer Certificate For:

- D-value
- Z-value
- Other



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Biological Indicators













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Chemical Indicators

EU Annex 1, Section 8.44

▲ There should be a clear means of differentiating products, equipment and components, which have not been subjected to the sterilisation process from those which have.

Indicators such as autoclave tape, or irradiation indicators may be used, where appropriate, to indicate whether or not a batch (or sub-batch material, component, equipment) has passed through a sterilisation process. However, these indicators show only that the sterilisation process has occurred; they do not indicate product sterility or achievement of the required sterility assurance level. **Chemical Indicators**

- Process indicator
- Not an indication of product sterility









Chemical Indicators

ISO 11140-1 CI Types	CI Description
Type 1	Process Indicators
Type 2	Specific-Use Indicators
Туре 3	Single-Variable Indicators
Type 4	Multi-Variable Indicators
Type 5	Integrating Indicators (Integrators)
Туре 6	Emulating Indicators (Cycle Verification Indicators)



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Chemical Indicators

EU Annex 1, Section 8.61

There should be adequate assurance of air removal prior to and during sterilisation when the sterilisation process includes air purging (e.g. porous autoclave loads, lyophilizer chambers). For autoclaves, this should include an air removal test cycle (normally performed on a daily basis) or the use of an air detector system. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.



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Air Removal Verification

- Bowie Dick Test
- Performed daily



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Sterilized Equipment Protection

EU Annex 1, Section 8.46

Suitable protection after sterilisation should be provided to prevent recontamination. If sterilized items are not used immediately after sterilisation, these should be stored using appropriately sealed packaging and a maximum hold time should be established. **Sterilization Wrapping**

- Microbial barrier
- Validated hold times





Transportation and Assembly of Sterilized Equipment

EU Annex 1, Section 8.47

G Where materials, equipment, components and ancillary items are sterilised in sealed packaging and then transferred into grade A, this should be done using appropriate validated methods (for example, airlocks or pass-through hatches) with accompanying disinfection of the exterior of the sealed packaging. The use of rapid transfer port technology should also be considered. These methods should be demonstrated to effectively control the potential risk of contamination of the grade A and grade B areas and, likewise, the disinfection procedure should be demonstrated to be effective in reducing any contamination on the packaging to acceptable levels for entry of the item into the grade B and grade A " areas.





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Material Transfer Airlocks/ Decontamination

- 4.5: Requirements for equipment surfaces, cleanability
- 4.6: Requirements for minimizing accumulation of particles, impurities, contamination
- 4.7: Design to minimize creation of particles
- 4.10: Requirements for controlling, monitoring and maintaining contamination control in material transfer
- 4.11: Requirements and preferences for transfer of materials
- 4.12.ii. Requirements for material airlocks & materials / operations
- 4.13: Requirements for critical interlocks, monitoring and alarm systems for preventing contamination through airlocks
- 4.15: Requirements for airflow patterns in cleanrooms mitigating ingress from lower grade area to higher
- 4.16: Requirements for monitoring pressure differentials / differences between cleanrooms / areas / isolators
- 4.25: Qualification and testing requirements for cleanrooms and equipment
- 6.6: Installation requirements for cleanroom & equipment utilities & technical areas





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Material Transfer Airlocks/ Decontamination

4.12.ii. Requirements for material airlocks and materials / operations



- Approved list of materials only for grade A transfer
- Transferred materials should be protected (= protective outer layers)
- CCS and appropriate risk assessment in place
- Specific disinfection and monitoring program in place for equipment
- Protective measures in place with the equipment to mitigate any risk of ingress to higher grade
- Cleaning and disinfection of transfer material loads as required



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Line Assembly – RABS/Isolator

EU Annex 1, Section 5.5

For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components).

Do not rely on environmental decontamination of the RABS/isolator using VHP[®] for sterilization of sterile processing stream.





Line Assembly – RABS/Isolator – Stopper Bowls







Line Assembly – RABS/Isolator – Filling Needles





Autoclave Sterilization









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Line Assembly – RABS/Isolator

Best Practice Recommendation

Stage wrapped/covered parts in RABS/isolator prior to environmental decontamination process (VHP®), unwrap/uncover sterilized parts through glove ports following decontamination aeration.





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Contamination Control Strategy

EU Annex 1, Section 2.3: A Contamination Control Strategy (CCS) should be implemented across the facility in order to define all critical control points and assess the effectiveness of all the controls (design, procedural, technical and organisational) and monitoring measures employed to manage risks to medicinal product quality and safety. The combined strategy of the CCS should establish robust assurance of contamination prevention. The CCS should be actively reviewed and, where appropriate, updated and should drive continual improvement of the manufacturing and control methods. Its effectiveness should form part of the periodic management review.





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Contamination Control Strategy



EU Annex 1, Section 2.4: Contamination control and steps taken to minimize the risk of contamination from microbial, endotoxin/pyrogen and particle sources includes a series of interrelated events and measures. These are typically assessed, controlled and monitored individually but their collective effectiveness should be considered together.





Thank you!

Questions?