Table 2 — Media fills – Initial performance qualification

Minimum number of simulations	Number filled / simulation	Contaminated units in any one simulation	Simulation runs affected by contaminated units	Action
3	< 5000	≥ 1	≥ 1	Investigation, corrective measures, restart validation
3	5,000 to 10,000	1	1	Investigation, consideration of repeat of 1 media fill
		> 1	> 1	Investigation, corrective measures, restart validation
3	> 10000	1	1	Investigation
		> 1	> 1	Investigation, corrective measures, restart validation

Table 3 — Media fills - Periodic requalification

Minimum number of simulations	Number filled	Contaminated units	Action
2 per year and line configuration	< 5.000	1	Investigation, revalidation
	5.000 to 10.000	1	Investigation, consideration of repeat media fill
		> 1	Investigation, corrective measures, revalidation
	> 10.000	1	Investigation
		> 1	Investigation, corrective measures, revalidation

10.10 Sterility testing

10.10.1 General

Where sterility testing is required for aseptically filled products, this testing shall be conducted for each batch or lot. The pharmacopoeial sterility tests are used when the method is applicable. When the pharmacopoeial test cannot be used the manufacturer shall specify the method applied.

NOTE 1 Examples of pharmacopoeias include Ph. Eur., JP and USP.

NOTE 2 In certain jurisdictions approval of non-pharmacopoeial sterility tests is required by the relevant competent authorities.

10.10.2 Investigation of sterility test positive units

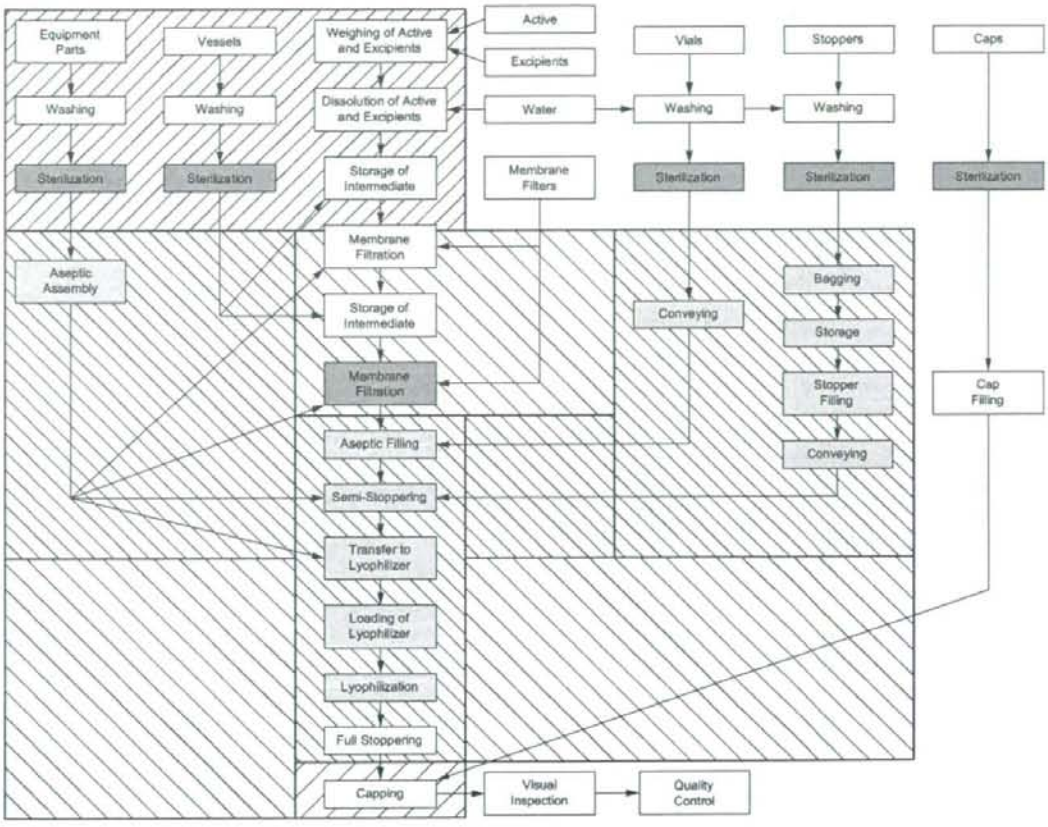
10.10.2.1 Positive sterility testing results shall be evaluated and an investigation shall be initiated to determine the source of contamination, including whether the growth occurred due to contamination during the test.

10.10.2.2 A correlation assessment between types of microorganisms found in the manufacturing environment, the sterility testing room and isolated from failed sterility test units shall be conducted.

NOTE Further guidance on the investigation of organisms isolated from a failed sterility test can be found in the pharmacopoeias.

Annex A
(informative)

Example of a flow chart



Annex B
(informative)

Comparison of classification of clean rooms

In ISO 13408-1 reference has been made to ISO 14644-1 classification only. This annex gives information on other regional and/or national classification systems.

Table B.1 — Classification systems

Classification according to				
ISO 14644-1 (particles >0,5µm/m³)	**ISO 13408-1**	**FDA**[a]	**EU GMP Guide Annex 1**[b] (in operation)	**EU GMP Guide Annex 1**[b] (at rest)
5 (3.520)	Critical processing zone	100 / M 3.5	Grade A	Grade A and B
6 (35.200)	Not defined	1.000 / M 4.5	Not defined	Not defined
7 (352.000)	Direct support zone	10.000 / M 5.5	Grade B	Grade C
8 (3.520.000)	Indirect support zone[c]	100.000 / M 6.5[c]	Grade C	Grade D
			Grade D	

[a] FDA Guidance for aseptic processing, September 2004

[b] EU GMP Guide, Annex 1:2003 (drafted revision 2005) refers to ISO 14644 but limits for non-viable particles are defined differently.

[c] Activities performed in these zones are split in the EU GMP Guide, Annex 1 into Grade C and D.

Annex C
(normative)

Specification for water used in the process

C.1 Potable water

C.1.1 Potable water shall be the starting material for the manufacture of purified water qualities used in aseptic manufacturing. Other use of potable water shall be restricted to cleaning purposes outside of the APA, for drinking faucets and for washing of hands in gowning rooms.

C.1.2 A specification shall be established and documented for potable water. Due account shall be taken of local legislation relating to the quality of potable water in setting this specification.

C.2 Treated potable water

C.2.1 If potable water is given additional treatment to reduce further the bioburden, then strict separation shall be maintained between such water and untreated potable water.

NOTE 1 Suitable additional treatments can include ozonation or chlorination as an initial step.

NOTE 2 Treated potable water can also be used in certain circumstances such as spray coolant in such autoclaves where the coolant can not be sterilized e.g. by recirculating throughout the autoclave.

C.2.2 Treated potable water for spray cooling during autoclave cycles shall be monitored frequently for microbial content and of activity of added substance(s).

C.3 Purified water

C.3.1 Purified water can be used in initial rinsing of components, equipment, closures etc. Purified water can be used as an ingredient in certain non-parenteral products, e.g. contact lens solutions. Purified water shall conform to the requirements for purified water given in the national and regional pharmacopoeias.

C.3.2 The microbial content shall be monitored and controlled to a limit appropriate to the intended use of the water as may be required by applicable regulatory or pharmacopoeia specifications.

C.3.3 Purified water distributed in fixed systems shall be circulated or kept in motion to minimize the formation of biofilm inside pipes and tanks. The system shall be sanitized according to a specified and documented frequency.

C.3.4 The water distribution system shall be designed to avoid areas where water does not flow freely and shall not allow water to stagnate.

C.3.5 If bacteria retentive filters are used in the system they shall be sterilized, integrity tested, and shall be changed according to a defined frequency and procedure. Filters of other porosities, e.g. particulate retentive filters, if used, shall be changed at a defined frequency.

C.3.6 Tanks and distribution systems for purified water should be constructed from stainless steel suitable for the intended use. Plastic systems should be avoided since they require more frequent sanitization.

C.4 Water for Injections (WFI)

C.4.1 Water for Injection shall be used for formulation of parenteral products including certain medical devices and in final rinsing of components, equipment, closures etc for the manufacture of such products

NOTE Examples of relevant medical device applications include injectable products such as collagen injections and viscoelastic products.

C.4.2 The feed-water to the WFI distillation equipment shall be pretreated appropriately. Attention should be paid to bioburden and/or endotoxin levels in the feedwater.

The composition of the incoming potable water should determine the choice of subsequent pretreatment steps. If chlorine is present, the use of a carbon bed should be considered. If colloids, organic substances or silicates in the potable water can penetrate the ion exchangers, additional steps like single or double pass reverse osmosis units can be employed as additional steps. It is recommended that the feed water is circulated in order to minimize the formation of biofilm.

C.4.3 WFI in distribution systems shall be kept at > 70 °C and circulated within a loop. The system shall be designed to avoid areas where water does not flow freely, and shall not allow water to stagnate. The temperature should be minimally be monitored and recorded at the end of the return loop.

C.4.4 The WFI distribution system shall be made of stainless steel suitable for the intended use. Its suitability shall be documented in the design qualification. Guidelines, e.g. ISPE Baseline, may be consulted for design aspects of finish, welding, slope etc.

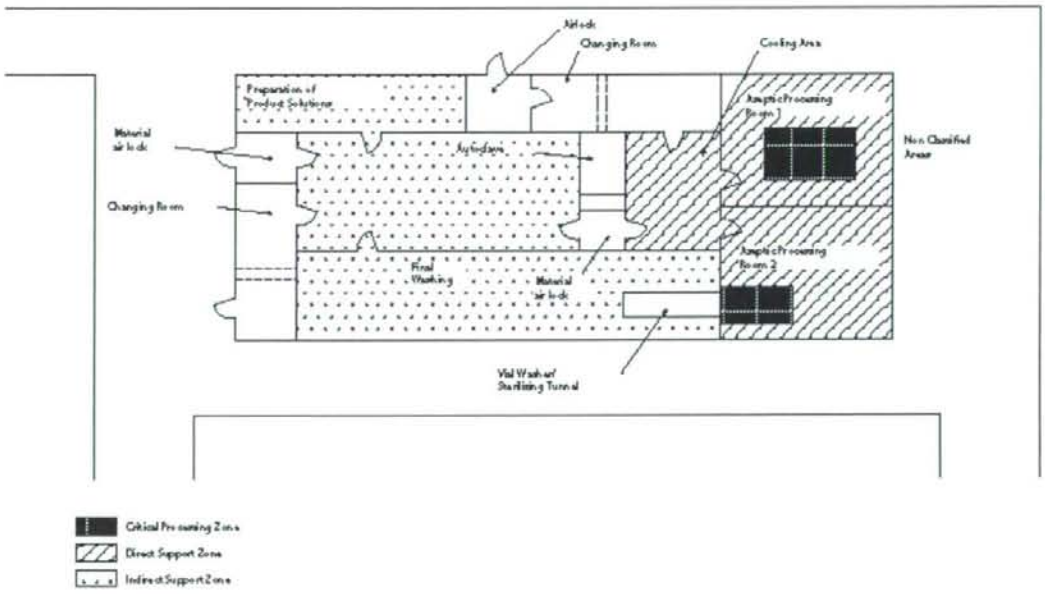
C.4.5 Frequent monitoring of bioburden and endotoxins shall be undertaken at least once every 24 h during processing Conductivity shall be monitored continuously and compared with defined limits. Specified and documented monitoring shall be performed on all use points where water can be drawn from the system.

C.4.6 Disinfection or sanitization of the WFI system shall be undertaken according to a defined procedure and frequency, and after a system breach or after a system integrity failure. If chemicals are used in the cleaning/disinfection/sanitization process their removal from the system shall be validated and confirmed.

WFI systems recirculating continuously at 80 °C may not require periodic disinfection unless a system breach or integrity failure has occurred. However, provisions are recommended for heating up to e.g. 95 °C under certain circumstances.

Annex D
(informative)

Aseptic Processing Area



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USP, Unites States Pharmacopeia, www.usp.org

ISPE, Baseline Guide, http://www.ispe.org/index.ww

別紙4

研究成果の刊行に関する一覧表

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