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GMP Series

Aseptic Processing of Sterile Medicinal Products

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1 Introduction

Here you will find answers to the following questions:

- What requirements are rooms and personnel expected to meet for aseptic processing?
- How is the bioburden reduced by means of sterile filtration?
- How is sterile filtration validated?
- How is the aseptic filling method proved?
- What interventions should take place in the processes?
- What must be borne in mind with respect to personnel qualification in the context of media fills?
- What measures must be taken when acceptance criteria are exceeded in the context of media fills?

In Europe aseptic processing is only accepted as a last resort when all possible methods of sterilisation in the final container have been adequately examined. When sterile medicinal products are manufactured, the European Pharmacopoeia requires that clear priority be given to sterilisation in the final container. In the Annex of the *Note for Guidance on Development Pharmaceutics* the European Medicines Agency (EMA) also very clearly states that aseptic processing should be the last option to be used when all other sterilisation methods in the final container have been excluded. The guidance however points out that heat-labile packaging material cannot in itself be the sole reason for adopting **aseptic processing** to prepare sterile medicinal products.

Fundamental differences exist between aseptic processing of sterile medicinal products and the manufacturing of sterile medicinal products using terminal sterilisation.

Terminal sterilisation normally also includes the filling and sealing of product containers in rooms with high cleanliness grades. The products are filled and sealed in this environment. The particulate and microbial loads (bioburden) of the intermediate product are thus minimised. At the same time it is ensured that the subsequent sterilisation process is successful. In most cases the product and primary packaging material have a low bioburden, but they are not sterile. The product then undergoes a sterilisation process in the final container.

With an aseptic process, the medicinal product, container and closure first of all undergo appropriate sterilisation processes separately and are then combined (see figure 1). However, as the product cannot be sterilised in its final container, it must be filled and sealed in an ultrapure environment.

Aseptic processing thus comprises a large number of individual work steps. The entire process is only as good as the individual process step which entails a risk. In order to achieve the goal of manufacturing a sterile product, several individual aspects must be borne in mind and validated individually in the context of aseptic processing. At the end process validation is performed by means of media fill and permits a final judgement to be made regarding the suitability of the process.

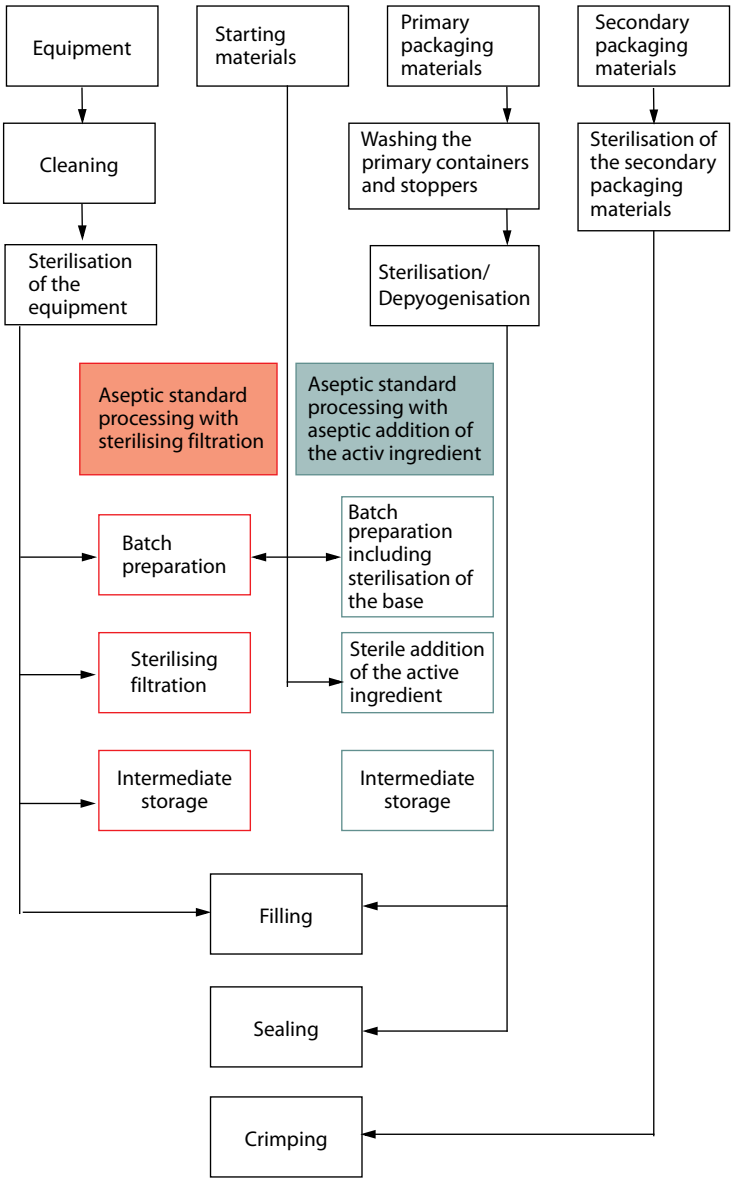

Figure 1 *Schematic diagram of aseptic processing by means of sterile filtration and the addition of sterile active ingredients*

cally only the single-layer and homogeneous double-layer filters consist of uniform material. A heterogeneous design has now become standard for the double-layer filters. The integrated fibre support permits greater mechanical load capacities to be achieved. The advantage is that individual large pores are blocked (see figure 2).

Candle filters are even more heterogeneous in design. In addition, they contain a whole range of membranous surfactants, softeners and other additives. The manufacturers must specify these soluble components of their filter materials. As part of validation, appropriate analytical methods must be used to test for these **extractables**. If this presents technical difficulties in operation, the extraction data can also be taken from the filter manufacturers' technical reports or validation documentation.

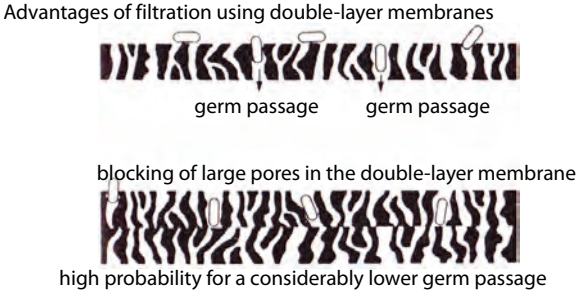

Figure 2 *Method for blocking large pores with the help of double-layer membranes (from Wallhäusser K.H. Praxis der Sterilisation, Desinfektion und Konservierung (Practice of Sterilisation, Disinfection and Preservation). 5th edition 1995, Thieme Verlag).*

It is equally important to monitor the possible adsorption of active pharmaceutical ingredients to the membrane material, which may possibly reduce the active ingredients in the product.

5.2.1 Filter devices

What type of filter is used depends on the product and the process. Sterile filtration is a difficult matter and requires intensive tests to determine which filter is best suited for the particular application.

The following types of filter devices are available:
- Disc filters
- Filter candles and
- Cartridges

Disc filters must be equipped with membrane filter layers by the user. This also applies for candle filters that have to be fitted in a filter housing. Cartridges are supplied by the manufacturer and are membrane filter layers (0.2 µm, 0.45 µm, 1.2 µm, etc.) that are

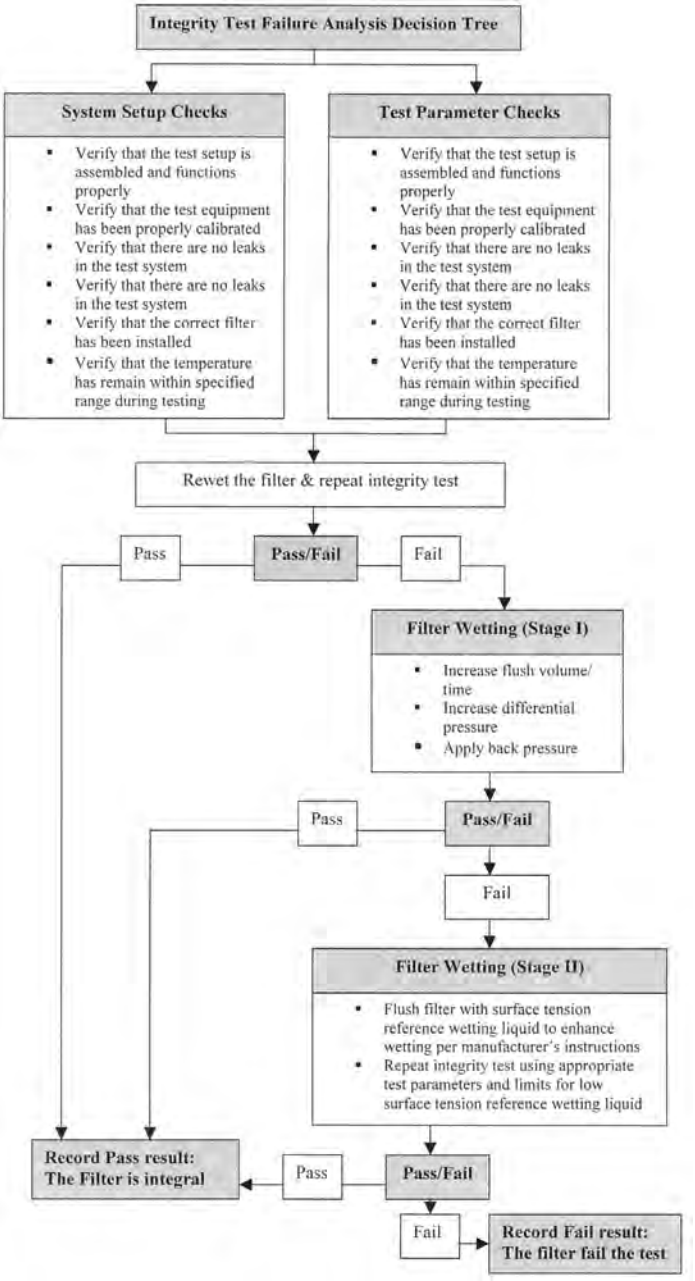

Figure 3 *Integrity Decision Tree (from: PDA Technical Report No 26)*

Worst-case validation conditions		
	Process conditions	**Validation conditions**
Product	AB 12	CD 13
Filter type/Item number	Durapore 0.2 µm/123456	Durapore 0.2 µm/ 123456
Sterilisation conditions	123 °C, 35 min (1 cycle)	123 °C, 35 min (1 cycle)
Number of filters	1	3
Filtration area per filter	0.2 m^2 (2,000 cm^2)	0.015 m^2 (150 cm^2)
Filtration volume per filter	Less than/equal to 500 L	Greater than/equal to 45 L (by means of recirculation)
Filtration volume per cm^2 filtration area	Less than/equal to 0.25 L	Greater than/equal to 0.3 L (by means of recirculation)
Contact time for product/filter	Less than/equal to 3 hr.	Greater than/ equal to 3.5 hr.
Filtration pressure	Less than/equal to 1.5 bar	Greater than/ equal to 1.5 bar
Flow rate per filter	Less than/ equal to 200 l/hr.	Greater than/ equal to 15 l/hr.
Flow rate per cm^2 filtration area	Less than/ equal to 10 ml /hr.	Greater than/ equal to 100 ml /hr.
Temperature range	20 to 25 °C	20 to 25 °C

Figure 8 Worst-case validation conditions

These tests complete filter qualification and product-/process-specific validation. The PDA provides detailed guidance for validating sterile filtration processes in Technical Report no. 26 *Sterilizing Filtration of Liquids*.

Any **inspection** of a sterile filtration process should address the following aspects:

- An SOP must exist for the filter integrity test.
- The filter integrity test device has been qualified according to GAMP category 3.
- The filter integrity test device is regularly calibrated (pressure and flow rate).
- A logbook must exist for the device.
- Failed tests have been examined and processed in accordance with an SOP. The deviation has also been processed in accordance with an SOP.
- The process has been validated (on both the filter manufacturer and medicinal product manufacturer sides).

In particular for the last point, section 5.1.3 of the PIC/S PI 007 Guideline provides information on selecting worst-case key formats. It states: "*Worst case conditions are often thought to be the largest container with the widest mouth as it is exposed longer to the environment. However, there are exceptions to this and one of them is small ampoules run at the highest speed as the ampoules may be unstable and cause frequent jams, thus necessitating frequent operator intervention.*"

Generally the principle has become established that the largest containers with the longest fill time and the smallest containers with the highest fill speed and the largest number of expected interventions represent the worst-case situations.

In addition to a clear definition of the **interventions**, the manner of carrying out interventions by appropriately trained personnel should also be evaluated regularly. This evaluation should be recorded in writing in a filling log. This check, which is required by the FDA, is also mentioned in the PIC/S PI 007 Guideline, where however a video as a possible form for this log is proposed. Although video recordings for this purpose may be more helpful than a written log, their confidentiality is not guaranteed and on account of the personal discretion they are disputed and must always be agreed on in advance with the works council and the management.

The PIC/S PI 007 Guideline provides information on simulation tests for specific aseptic manufacturing processes such as:

- Lyophilisates
- Suspensions
- Ointments
- Powders

6.3.3 Number of units

The simulation run sizes should be adequate to mimic commercial production conditions and accurately assess the potential for commercial batch contamination. The number of units filled during the process simulation should be based on the contamination risk for a given process and sufficient to accurately simulate activities that are representative of the manufacturing process[23].

The number of units to be filled is thus largely based on the number routinely filled. The specifications of the various guidelines are shown in figure 9.

The line speeds of today's filling lines however permit daily batch sizes which are multiples of the guidelines' specifications. Consequently in practice a minimum quantity of 10 to 15% of the maximum daily batch size has become established. This approach represents a contribution to reach the objective of a *zero-level* of failures.

23. FDA Guidance for Industry: Sterile Drug Products produced by Aseptic Manufacturing – Current Good Manufacturing Practice; 2004

Guideline	Number of units to be filled
EU GMP Guide and PIC/S PI 007 Guideline	An adequate number of units; For small batches, the number of containers used for the media fill should be at least as high as for the product batch
ISO 13408	At least 3,000 units
FDA Aseptic Guide	5,000 to 10,000 units

Figure 9 Specified number of units to be filled

6.3.4 Fill volume per unit

The fill volumes are based on the quantity required to wet the entire inner surface of the primary packaging material with culture medium. Consequently the following aspects have to be considered when establishing the fill volume:

- All surfaces of the container used and, if required, of the stopper must be wetted.
- Microbial growth must be detectable (here it makes sense to halve the nominal volume, as in the second incubation stage the containers should be turned to comply with the above-mentioned requirement of completely wetting the containers.
  Casein soya peptone has a tendency to foam, which leads to the containers overflowing when the fill volume is set too high. This is also avoided by reducing the fill volume by half.)
- The fill volume must be adjusted to the growth conditions of the microorganisms (anaerobic and aerobic). The following procedure is appropriate here:
  - Aerobic conditions – half nominal volume,
  - Anaerobic conditions – full nominal volume.

6.3.5 Fill time

No uniform specifications are provided by the authorities to determine the fill time. Thus, for instance, for lengthy filling operations (e.g. more than 24 hours) PIC/S PI 007 recommends that simulation filling should be extended to this period. In Annex 1 the EU GMP Guide makes no concrete statement on this subject. The same applies to the FDA, which only requires a justification of the fill speed or of the fill time resulting from it.

Usually, the worst-case filling speed is considered the filling speed which leads to the longest exposure of a medicinal product and its primary packaging material to the aseptic environment. In the best case, this scenario also involves the worst-case container (largest opening and highest fill volume). The smallest container will have the fastest fill speed as only a small volume is filled. The largest container in the portfolio will have the lowest fill speed because a large volume has to be filled. If no worst-case fill speed can be determined, a worst-case fill speed can be simulated. Thus, for instance, the lowest fill speed from routine operation can be halved to produce the worst-case situation.

6.3.6 Preparing and performing the media fill

A helpful overview of preparation, implementation, documentation and reporting of a media fill is provided in figure 10.

Preparing and performing a media fill	
Microbiology	• Culture medium exists and has been checked (nutritive properties) • Endotoxin content determined (if required) • Incubation capacity available • Monitoring plans up to date • Monitoring personnel informed and trained • Personnel for optical control informed, trained and checked
Intervention simulation	• Have all routine interventions been planned (e.g. glass breakage, transport jam, needle change, split pipe, empty run and restart after interruption, etc.)? • Have all routine activities been planned (e.g. replenishing stoppers, interruptions, attaching and removing bulk bins, breaks, etc.)?
Personnel	• Who will take part? Are all participants present? • Have all staff members been informed of the date? • Is the appropriate clean room clothing available for each member of staff (also for XS or XXXL staff members)? • Does a time schedule exist for their work? • Have shift models been mapped? • Do they all have access authorisation? • Have they all undergone a health check and appropriate training? • Do all members of staff have a valid qualification status?
Checks	• Process monitoring with log (details of who did what and how) • Possibly video log
Documentation	• Date, room, filling system, time (start, end) • Culture medium, batch, use-by date • Containers, seals • Medium volume per container, fill speed • Filter type, filter integrity test, tunnel temperature diagram • Fault simulation (what, when, who, counter reading) • Participating staff • Performing monitoring (who, what, when) • Reconciliation
Reconciliation	• Number of containers used • Number of filled containers (line set up) • Number of filled containers (process) • Number of containers rejected during optical check • Number of containers supplied for incubation • Number of containers checked optically • Number of containers with growth

Figure 10 Preparing and performing the media fill

7 Author

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2001–2002 WDT eG:
Cooperation on reorganization of sterile areas. Key area: Qualification of facilities and equipment. Compilation of VMPs and SOPs.

2002–2004 WDT eG:
Qualification Manager for rooms and facilities. Key area: Qualification of high-purity water systems and distribution sys-tems. Cleaning Validation Manager. Planning and controlling of main-tenance, calibration and requalification of GMP-relevant facili-ties and equipment. Project Coordinator: Reconstruction of a weighing centre according to GMP.

2004–2006 WDT eG:
Additionally, coordinator of various projects in the area of industrial engineering: Energy monitoring, improvement of in-frastructure in the area of steam production, heating and cooling, as well as their distribu-tion. Reconstruction of a laboratory ventila-tion system. Construction, implementation and qualification of a building control system accord-ing to GMP.

since 2006 WDT eG:
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since 2009 Member of the International Association for Pharmaceutical Technol-ogy

since 2009 Member of the Association of German Engineers (VDI)