Manufacturing Sterile Products to Meet EU and FDA Guidelines

By Ruven Brandes, Martin Mayer, Dr. Hanfried Seyfarth and Dr. Margit Gieseler
# Manufacturing Sterile Products to Meet EU and FDA Guidelines

## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>About the Authors</td>
<td>2</td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
</tr>
<tr>
<td>Air Lock Concepts</td>
<td>10</td>
</tr>
<tr>
<td>Manufacture of Terminally Sterilized Products</td>
<td>19</td>
</tr>
<tr>
<td>Sterilization Processes</td>
<td>45</td>
</tr>
<tr>
<td>Aseptic Processing</td>
<td>75</td>
</tr>
<tr>
<td>Freeze-drying</td>
<td>105</td>
</tr>
<tr>
<td>Microbiological Monitoring</td>
<td>117</td>
</tr>
<tr>
<td>Appendices</td>
<td>148</td>
</tr>
</tbody>
</table>
About the Authors

Ruven Brandes is a biological process engineer who has extensive experience managing the engineering, qualification, cleaning validation, clean room ventilation, calibration, monitoring systems (production and storage), maintenance and servicing of sterile areas and equipment used in the production of medicinal products. He is a member of the International Association for Pharmaceutical Technology, as well as the Association of German Engineers (VDI).

Dr. Margit Gieseler holds a doctorate in pharmaceutical technology and has worked for Boehringer Ingelheim in pharmaceutical development. She is the CEO of Gilyos, which specializes in freeze-drying process design and optimization, physicochemical characterization of materials (freeze-dry microscopy), assessment of the morphology of freeze-dried products (specific surface area, scanning electron microscopy), technical consulting for freeze-drying equipment, operational qualification and performance testing.

Martin Mayer has worked for Fresenius in quality assurance, SOP management, pharmaceutical-technical qualification and key accounting, and Fresenius Kabi in product partnering, contract manufacturing and project management. He has also worked for Pharmaplan and Fresenius Kabi in senior positions in quality management and GMP compliance and consulting for pharmaceuticals and medical devices. He is an expert on HVAC systems and clean rooms.

Dr. Hanfried Seyfarth has decades of expert experience as head of the departments of microbiology, quality control and process assurance at Boehringer Ingelheim.
Introduction

The sterility of a drug is defined as the complete absence of viable microorganisms. Testing for sterility of a preparation is evaluated statistically, creating a Sterility Assurance Level (SAL) (according to the European Pharmacopeia 6, Main Volume 2008, Part 2.6.1). The SAL describes the probability of nonsterile units occurring in a single batch of sterile medicinal product. According to the pharmacopeia, the SAL for sterilized drugs in the final container is indicated as $1 \times 10^{-6}$. This corresponds to a 6-log reduction of the microbial population.

Due to the specific requirements for the manufacturing of sterile products in order to minimize the contamination with microorganisms, particles and pyrogens, all requirements, as shown in Figure 1 should be complied with.

**Figure 1**

<table>
<thead>
<tr>
<th>General Requirements for the Manufacturing of Sterile Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Qualified and well-trained personnel</td>
</tr>
<tr>
<td>• Suitable premises</td>
</tr>
<tr>
<td>• Suitable production equipment</td>
</tr>
<tr>
<td>• Validated methods for all critical manufacturing steps</td>
</tr>
<tr>
<td>• Documentation of environmental conditions and in-process controls</td>
</tr>
</tbody>
</table>

There are two ways to manufacture sterile medicinal products:

• Terminal sterilization

• Aseptic processing

For the manufacturing of sterile medicinal products, the European Pharmacopoeia requires that terminal sterilization be used whenever possible (Ph. Eur. 6, Main Volume 2008, Part 5.1.1). In the annex to the *Note for Guidance on Development Pharmaceutics (EMA, NFG-Development Pharmaceutics, Para 5, Manufacturing Process)* issued by the European Medicines Agency (EMA), aseptic processing is defined as a method that should be used only as a last resort. This assumes that all other possible sterilization methods in the final container have been excluded before. The pharmacopeia as well as the *Note for Guidance on Development Pharmaceutics* point out that the primary packaging of the medicinal product has to be taken into account when choosing the sterilization method. A lack of thermal resistance of a primary packaging material should not in itself be considered as adequate justification for using aseptic processing. The obligation to investigate the use of alternative packaging material is clearly referred to.

In the annex to the *Note for Guidance on Development Pharmaceutics*, the decision trees shown are intended to assist in the selection of an appropriate sterilization method for each product (see Figure 2 and Figure 3).
Manufacturing Sterile Products to Meet EU and FDA Guidelines

Figure 2

Decision Tree for the Sterilization of Aqueous Products

Can the product be sterilized by moist heat at 121°C for 15 minutes?

No

Can the product be sterilized by moist heat with F₀ ≥ 8 minutes achieving SAL of ≤10⁻⁶?

No

Can the formulation be filtered through a microbial retentive filter?

No

Use pre-sterilized individual components and aseptic compounding and filling.

Yes

Use autoclaving at 121°C for 15 minutes.

Yes

Use moist heat with F₀ ≥ 8 minutes.

No

Use a combination of aseptic filtration and aseptic processing.

Yes

Use sterilization with an absorbed minimum dose of ≥25 K Gy.

No

Can the formulation be filtered through a microbial retentive filter?

No

Use pre-sterilized individual components and aseptic compounding and filling.

Yes

Use filtration and aseptic processing.

Figure 3

Decision Tree for the Sterilization of Nonaqueous and Other Products

Can the product be sterilized by dry heat at 160°C for 120 minutes?

No

Can the product be sterilized by dry heat with an alternative combination of time and temperature to the standard cycle achieving an SAL of ≤10⁻⁶?

No

Can the product be sterilized by a method different from dry heat, such as ionizing radiation, with an absorbed minimum dose of ≥25 K Gy?

No

Can the formulation be filtered through a microbial retentive filter?

No

Use pre-sterilized individual components and aseptic compounding and filling.

Yes

Use sterilization by validated irradiation dose.

No

Use sterilization with an absorbed minimum dose of ≥25 K Gy.

Yes

Use sterilization by validated irradiation dose.
The decision trees refer to aqueous, nonaqueous or semisolid and dry powder products and are intended to assist in the selection of the optimal sterilization methods for the product. Both decision trees initially require a standard method. If this is not possible one has to move down the decision tree. If a suggested alternative approach is feasible, it must be applied.

Aseptic processing is mentioned as a last option. The choice of an alternative sterilization method as well as the reasons for choosing aseptic processing must therefore be clearly documented, explained and scientifically justified. The selected sterilization method must be appropriately validated to guarantee the highest level of sterility.

**Manufacturing of Terminally Sterilized Products**

The manufacture of terminally sterilized products takes place under controlled environmental conditions. The manufacture comprises various process steps such as the formulation (optionally filtration), filling and sealing. These operations are intended to minimize the risks of microbial or particulate contamination of the intermediates to guarantee the success of subsequent sterilization.

The following methods may be selected for carrying out the sterilization process:

- Steam sterilization (heating in an autoclave)
- Dry heat sterilization
- Radiation sterilization

The cleanliness grades with the corresponding environmental conditions for the individual manufacturing operations are determined in *Annex 1* of the *EU GMP Guide* as shown in Figure 4.

**Figure 4**

<table>
<thead>
<tr>
<th>Manufacturing Operations</th>
<th>Room Classes According to the <em>EU GMP Guide, Annex 1</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Preparation of solutions and components for subsequent filling</td>
<td>• Grade D zone</td>
</tr>
<tr>
<td>• Background environment for blow/fill/seal equipment</td>
<td>• Manufacturing zone for less critical process steps</td>
</tr>
<tr>
<td>• Filling of products for terminal sterilization</td>
<td>• Grade C zone</td>
</tr>
<tr>
<td>• Preparation of solutions where the product is at a high or unusual risk of microbial contamination</td>
<td>• Manufacturing zone where the operation represents an unusual risk</td>
</tr>
<tr>
<td>• Preparation and filling of ointments, creams, suspensions and emulsions</td>
<td>• Grade A zone</td>
</tr>
<tr>
<td>• Filling of products where the product is at a high or unusual risk of microbial contamination</td>
<td>• For critical process steps with a high level of risk</td>
</tr>
</tbody>
</table>
Aseptic Processing

The pharmacopeia (Ph. Eur. 6, Main Volume 2008, Part 5.1.1) describes aseptic processing as follows:

“The aim of aseptic processing is to maintain sterility of a preparation made of sterilized components. This means that the starting materials required for manufacture including primary packaging materials, should wherever possible be sterilized prior to aseptic processing and that contamination during manufacture must be prevented.”

The Institute for Applied Healthcare Sciences in Germany describes aseptic processing as follows:

“Aseptic processing constitutes a working technique which generally consists of several coordinated processing steps. Each processing step should make optimum use of all options to reduce the number of germs to contribute to the resulting aim, i.e. a sterile product.” (IFAHS, 2003)

Preparation and follow-up of the whole aseptic manufacturing process strongly influence the quality of the product. The importance of complying with these quality influencing operations within aseptic processing is also clearly stated in Annex 1 of the EU GMP Guide under Processing (Points 64 to 82).

This is why various aspects have to be taken into account for aseptic processing to guarantee optimum sterility.

These aspects are:

- Premises
- Air quality
- Personnel
- Hygiene

All these aspects should be qualified and validated separately. Finally, aseptic processing is simulated twice a year using a media fill. Process simulation with media is the final step of validation measures and allows a concluding assessment of the suitability of the process.

The cleanliness grades for individual process steps of aseptic processing are specified in Annex 1 of the EU GMP Guide (see Figure 5).
Sterilization Procedures

Sterilization of individual components of the product should be validated. Different methods are used for product solutions, primary packaging and closures. There are several possible methods:

- Sterile filtration for solutions,
- Dry heat sterilization for glass containers,
- Steam sterilization for closures.

GMP Regulations, Standards and Guidelines

When manufacturing a sterile medicinal product, current legislation and the state of the art in science and technology must be taken into account.

The most important guidelines and technical monographs that should be taken into account during aseptic processing of medicinal products and during the manufacture of terminally sterilized medicinal products will be listed in the following pages. The importance and the regulatory environment of some important guidelines will be briefly explained.