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Sterilisation Processes – Requirements and Definitions

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General Requirements

The current *Annex 1 of the EU GMP Guide* provides guidelines and minimum requirements for the manufacture of sterile products. Some of the requirements contained therein are also relevant for the manufacture of non-sterile products, where the control and reduction of contamination is important.

The manufacture of sterile products covers a wide range of product types, primary packaging materials and technologies. The general guidelines contained in Annex 1 must be followed in the design and control of facilities, equipment, systems and processes to prevent contamination of the final product with microorganisms, particles and endotoxins/pyrogens.

The *sterilisation process* used must be suitable and effective for the product or equipment. The repeatability and reliability of the process are verified using scientific data, and critical parameters are controlled, monitored and recorded.

The specified *sterilisation conditions* must be consistently achieved in all parts of the load or on the entire surface of the system, equipment and components. This is verified during validation by means of physical measurements and, if necessary, the use of suitable bioindicators (BI). Appropriate precautions must be taken to avoid secondary contamination. The population, purity and identity of the BI are verified before use. Further parameters (e.g. D-value, z-value) can be used from the batch certificate of the qualified BI supplier. Positive controls must be tested for each sterilisation cycle.

Relevant conditions such as product composition, storage conditions and intermediate product hold times must be taken into account in the validation studies.

The *equipment holding times* relevant for sterilisation and sterility must be validated for equipment, components and containers, e.g:

- the time between cleaning and sterilisation
- the time between sterilisation and use
- the time between the start of product preparation and its sterilisation/sterile filtration.

During sterilisation, the defined *routine operating parameters* (e.g. physical parameters, loading patterns) must be adhered to and recorded for each sterilisation process. Deviations from these validated parameters or failed sterilisation cycles must be investigated.

The *validity* of the sterilisation process must be verified at regular intervals. The various load patterns (e.g. minimum, maximum, worst-case load) or worst-case conditions (e.g. time, temperature) must be taken into account in the validation strategy and subjected to regular re-validation. "Worst-case" loads must be re-validated at least once a year for heat sterilisation processes. The defined validation conditions must be justified accordingly in the contamination control strategy (CCS).

Sterilised units must be clearly *marked* to distinguish them (e.g. product name, batch number, date, sterilisation status). It should be noted that optical indicators only show that the sterilisation process has been completed and do not provide any indication of the sterility of the product or that the required sterility assurance has been achieved.

To *prevent re-contamination,* the items to be sterilised must be protected in a suitable manner (e.g. sterile packaging/containers/transfer containers, overpressure). The packaging must be designed to be compatible with the selected sterilisation method and to minimize the risk of contamination by particles, microorganisms, endotoxins/pyrogens or chemicals. Validation should consider the integrity of the protective sterile barrier system, the maximum equipment holding time prior to sterilisation and the maximum shelf life of the sterilised units.

In order to reduce critical interventions and the risk of contamination, the current Annex 1 of the EU GMP Guide also refers to the *automation of sterilisation processes*, e. g. through *sterilisation in place* (SIP) or the use of dry heat sterilisation tunnels.

Definitions

By definition, absolute sterility cannot be achieved during sterilisation. Sterility is only guaranteed with a defined probability, as germs are killed according to mathematical laws. The probability of the presence of viable microorganisms after sterilisation is specified as the SAL value *(sterility assurance level)*.

Below you will find definitions of the most important terms from relevant regulations and standards.

What is a sterile product?

A sterile product is *"free from viable microorganisms"*. [1, 2]

"For purpose of this guidance, sterile product refers to one or more of the sterilised elements exposed to aseptic conditions and ultimately making up the sterile active substance or finished sterile product. These elements include the containers, closures, and components of the finished drug product. Or, a product that is rendered sterile by a terminal sterilisation process." [3]

What does sterility mean?

Sterility is described as *"a condition that is free of viable microorganisms"* [4, 5] or as *"the absence of living organisms"*. [6]

What is the Sterility Assurance Level (SAL)?

The SAL *"describes the probability of non-sterile units occurring in a product after sterilisation."* [7]

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[1] DIN EN 556 Sterilization of medical devices
[2] DIN EN ISO 14937 Sterilization of healthcare products
[3] EU GMP Guide – Guide to Good Manufacturing Practice, Annex 1: Manufacture of sterile medicinal products
[4] DIN EN 556 Sterilization of medical devices
[5] DIN EN ISO 14937 Sterilization of healthcare products
[6] EU GMP Guideline, Glossary
[7] PIC/S PI-007 Recommendation on the Validation of Aseptic Processes

What is meant by sterilisation?

"Validated process used to render a product free of viable organisms. Note: In a sterilisation process, the nature of microbiological death of reduction is described by an exponential function. Therefore, the number of microorganisms which survive a sterilisation process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero." [8]

What is terminal sterilisation?

"The application of a lethal sterilising agent or conditions to a product in its final container to achieve a predetermined sterility assurance level (SAL) of 10^{-6} or better (e.g. the theoretical probability of there being a single viable microorganism present on or in a sterilised unit is equal to or less than 1 x 10^{-6} (one in a million))."

What is a sterilisation process?

Sterilisation processes are "*a set of measures or working steps for meeting specific requirements for sterility. This series of measures or working steps includes preparation (if necessary), the treatment with the sterilising agent under specified conditions and all necessary follow-up*". [9]

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[8] PIC/S PI-007 Recommendation on the Validation of Aseptic Processes
[9] DIN EN ISO 14937 Sterilization of healthcare products

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