

1 Purpose

The purpose of this Guideline is to provide guidance on the manufacture and microbiological testing of sterile Investigational Medicinal Products (IMP) and Active Pharmaceutical Ingredients (API).

2 Scope and Applicability

The guideline applies to the manufacture of sterile products within R&D for human use and for stability studies intended to be filed with regulatory submissions. The guideline applies to aseptically processed as well as terminally sterilized products.

The provisions of this guideline additionally apply to contractors manufacturing sterile product for R&D.

In the context of this guideline product includes sterile API and formulated IMP. The guideline scope excludes pre-clinical materials. The guideline also does not include biological products and Active Pharmaceutical Ingredients produced by cell culture/fermentation, which will be covered in a separate guideline

3 Definitions

3.1 Active Pharmaceutical Ingredient (API)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product that when used in the production of a drug becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

3.2 Investigational Medicinal Product (IMP)

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a Clinical Study, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

3.3 Clean Area

An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area (Eudralex definition).

3.4 Controlled Area

An area where unspecialized product, in-process materials, and containers/closures are prepared (FDA definition).

5 Guideline

5.1 General

The manufacture of sterile products (Investigational Medicinal Products and Active Pharmaceutical Ingredients for the purposes of this Guideline) requires facilities that are suitably designed and qualified. Design features alone do not assure the quality of sterile products, especially those prepared aseptically, which additionally relies to a large part upon robust processes and procedures, and the training and experience of personnel.

Process qualification, taking into account related items such as operator gowning, sterile filtration, environmental controls, etc., is essential for sterile products manufacture. Specific consideration should be given depending on the type of process (e.g., aseptic processing, isolator, or blow/fill/seal technology).

Facility design philosophies, air classifications, environmental monitoring limits and other operational requirements are specified in Annex 1 of "The Rules Governing Medicinal Products in the European Union" and the FDA "Guideline on Sterile Drug Products Produced by Aseptic Processing". Additional guidance regarding specific engineering for facilities used in the manufacture of sterile products is to be found in the ISPE Baseline Pharmaceutical Engineering Guide Volume 3.

The ICH Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients indicates that applicable GMP guidelines for drug products, which are reflected in this guideline, generally would apply to the manufacture of sterile API.

The following guidance is provided only as a summary of requirements defined in the various regulations and technical papers on sterile manufacturing, and gives some additional points of clarification. The reference section includes a list of documents, which include detailed information on each of the areas discussed below and these should be consulted for more detailed guidance.

5.2 Sterilization Processes

- Aseptic processing of sterile products must only be employed when terminal sterilization in the final container is not possible.
- All product sterilization processes must be validated.
- All process validation including sterilization of equipment, utensils, containers and closures must be completed before material for clinical trials can be manufactured.
- Specific requirements for the periodic re-qualification of sterilization processes must be in place.
- Fixed loading patterns and cycles must be established for processes performing batch sterilization of product, components, and equipment.
- Sterilized items must be readily identifiable to avoid mix up with un-sterilized items.
- Cycle charts for sterilization processes must be reviewed and approved to ensure compliance of each cycle with validated process parameters.

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- Lyophilizer chambers must be sterilizable.

5.3.1 Sanitization and Cleaning

- Sanitization and cleaning programs must be in place and described in sufficient detail to ensure clean, sanitary and sterile (where appropriate) conditions.
- Equipment surfaces contacting sterile drug product or sterile containers and closures must be sterilized prior to each use.
- Validated equipment sterilization process must be used, with storage time limits.
- Written procedures for the use of pest control, sanitizing and cleaning agents must include provisions to prevent contamination of equipment, materials and product
- The efficacy of sanitizing agents must be qualified.
- More than one type of sanitizing agent must be employed on a rotating basis, and the efficacy of the sanitizing agent should be assured over time.
- Sanitizing agents used in critical areas must be sterilized before use.

5.3.2 Environmental Monitoring

- Environmental monitoring programs for viable organisms must be defined, and include monitoring types, locations, and frequencies.
- Environmental monitoring programs for non-viable particles must be defined including locations and frequencies.
- Facility monitoring programs, including temperature, humidity and pressure differentials must be in place.
- Environmental monitoring programs must include alert and action limits, defined responses to excursions, and periodic trends of monitoring results.
- Alert limits must reflect the limit of normal operating conditions in order to highlight possible shifts in conditions, and must be based on historical data where there is sufficient data to do this.

5.3.3 Personnel

- Clothing worn by operators, cleaning personnel, and support personnel must be appropriate for the operations carried out within each area of classification.
- There must be documented control over garment sterilization and use for critical areas.
- For operations carried out in critical areas, the use of face protection that minimizes the area of exposed skin must be adopted.
- Operators must undergo assessment of gowning competence both initially (before working in a critical area) and also at periodic re-qualifications.
- Operator gowning qualification for sterile operations must include microbiological assessments.
- Regular training, specific to the sterile manufacturing operations being performed, must be conducted, and include personnel health and hygiene

- terminated (i.e. PST cancellation policy) must be in place.
- Circumstances under which a satisfactorily filled unit can or cannot be discarded (i.e. container discard policy) must be described in procedures. Normally only containers identified as broken must be excluded from incubation after filling. All units which have been satisfactorily filled and closed must be incubated.
- -In-process checks must be simulated where appropriate, but filled containers must generally not be discarded unless they were not satisfactorily filled and closed.
- It may be beneficial to have trained observers who are independent from the production team monitor the PST, or portion of it. Written observations may be helpful in routinely providing feedback to operators in terms of good or poor aseptic techniques, or otherwise may provide valuable in the event of a PST failure.
- Consideration should be given to overlaying filled containers with compressed air rather than Nitrogen to avoid the production of anaerobic conditions preventing microbiological growth in a contaminated container.
- Any contaminated unit must be investigated.

5.5 Sterility Testing

Specific guidance for microbiological laboratories is given in the FDA -Guideline on Sterile Drug Products Produced by Aseptic Processing

- Collection of batch samples for sterility testing must follow established sampling plans to ensure that the containers chosen are representative of the critical parts of the process or sterilizer load.
- The microbiological testing laboratory environment for sterility testing of aseptically manufactured products must employ facilities, controls and monitoring comparable to those used for filling/closing operations.