Annex A3

Guidance on Process Validation Scheme for Terminally Sterilised Products

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1 PURPOSE

This guidance document is intended to provide guidance for the submission of information and data in support of the efficacy of terminal sterilization processes in product license application which is required in the dossiers.

This guidance document should be read in conjunction with the guidance listed below:

- Note for Guidance on Process Validation (EMA, 2001)
- Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products (FDA, 1994)
- Annex 4 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (Technical Report Series No. 957, 2010)
- EC Guide to Good Manufacturing Practice (Annex 1) March 2009
- Guide To Good Manufacturing Practice For Medicinal Products Annexes (PIC/S, September 2009)

2 SCOPE

This guidance document applies to the sterile drug product processed using terminally sterilization.

3 GENERAL INFORMATION

Sterilization can be achieved by the use of moist or dry heat, radiation with ionizing radiation, gases or by filtration with subsequent aseptic filling of sterile final containers.

Where possible and practicable, heat sterilization is the method of choice.

4 INFORMATION FOR TERMINAL STERILIZATION PROCESSES

In general, description of sterilization process and process validation data for the following items should be provided.

- Drug product in its final container-closure system
- Containers, closures, equipment and components
- Product intermediate

Where reprocessing (e.g. additional thermal processing) of drug product is allowed, supporting data should be provided.

4.1 Terminal Sterilization Process by Moist Heat

4.1.1 Process Description of Moist Heat Sterilization

A description of the autoclave process should be provided which includes:

- Identity of the autoclave (e.g. equipment number, manufacturer and model)
- Cycle type used (e.g. saturated steam, water immersion and water spray)

- Cycle parameters and performance specifications including temperature, pressure, time and minimum and maximum F_0

- Methods and controls used to monitor routine production cycles (e.g. temperature probes, chemical and biological indicators, leak test results) including the number and location of each as well as acceptance and rejection specifications [optional].

4.1.2 Process Validation and/or Evaluation of Moist Heat Sterilization

a. Heat Distribution and Penetration Study

Approach and specification used for heat distribution and penetration study as well as the summary of recent study results:

- Approach and specifications

- Diagrams showing the number of thermocouples, chemical indicators and/or biological indicators, which applicable, used, and their locations in the autoclave chamber

- Diagrams showing minimum and maximum load with identified cold spot(s)

- Results obtained from a minimum of three consecutive, successful cycles

b. Microbiological Challenge Study

A sterility assurance level (SAL) of 10^{-6} or better should be achieved for all parts of the finished drug product claimed to be sterile.

A summary report for microbiological challenge study, which may be combined with heat penetration study report, should be provided with the following:

- Bioburden data, especially when overkill approach is not used

- Certificate of Analysis (CoA) of biological indicators used, which should include information on identification, resistance and stability

- The resistance of biological indicators
  Resistance in or on the drug product (i.e. in the drug product solution, or on the surface of container or closure parts or interfaces) or drug product-substitute should be determined. If spore carriers, e.g. spore strips, are used, the resistance of spores on the carrier relative to that of directly inoculated drug product should be determined, if necessary.

- Results and conclusion of microbiological validation studies demonstrating the effectiveness of the minimum cycle to provide a SAL of 10^{-6} or better to the drug product under the most difficult sterilization conditions.

4.2 Other Terminal Sterilization Process

The types of information outlined in moist heat sterilization process are, in general, also applicable to sterilization by dry heat, gases, e.g. ethylene oxide and sterilization by radiation, e.g. gamma and electron beam.

As a minimum, the following information should be provided:

- Descriptions of load (pattern)
- Validation data in support of the efficacy of the minimum cycle
- Container-closure integrity
- Re-process, if applicable
- Sterilization process impact on the chemical and physical attributes of the drug substance or drug product, where applicable

Specific requirements are provided below for process validation of the sterilization by ethylene oxide and by radiation.

4.2.1 Ethylene Oxide (EO)

a. The decision to choose EO sterilization should be justified.

b. The sterilizer(s) and controlled site(s) for pre-humidification and aeration of the drug product load.

c. The parameters and limits for all phases of the cycle, e.g. pre-humidification, gas concentration, vacuum and gas pressure cycles, exposure time and temperature, humidity, degassing, aeration and determination of residuals.

d. The microbiological methods (growth medium, incubation temperature and time interval) for cultivating spores from inoculated samples during validation experiments.

4.2.2 Radiation

a. Radiation facility

b. The radiation source and method of exposure (i.e. movement through the irradiator)

c. Type and location of dosimeters used to monitor routine production loads

d. Packaging configuration data

e. Multiple-dose mapping studies

f. The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle

4.3 Container-Closure System (CCS) Integrity

In general, the following types of information and data in support of the microbial integrity of the drug packaging components should be provided:

a. Simulation of the Stresses from Processing

Experimental designs should simulate the stresses of sterilization process, handling and storage of the drug and their effects on the container-closure system. Physical, chemical and microbiological challenge studies may be necessary.

b. Demonstrate Integrity Following the Maximum Exposure

CCS integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s). If a drug product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design.

c. The Sensitivity of the Test [optional]

The sensitivity of the experimental method used for container closure integrity testing should be specified and provided.

5 GLOSSARY

Biological Indicator (BI):
A population of microorganism inoculated onto a suitable medium and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process.

Component
Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.

Terminal Sterilization:
Final sterilization of the drug product using steam heat and/or dry heat or radiation sterilization.

F_0 Value:
Equivalent amount of time in minutes at 121°C, which has been delivered to a drug product by the sterilization process. For example, 15 minutes sterilization at a reduced temperature of 111 °C produces a lethal effect, which is equivalent to 1.5 minutes at 121.0 °C