Annex A2

Guidance on Process Validation Scheme for Aseptically Processed Products

Table of content

1 PURPOSE

This guidance document is intended to provide guidance for the submission of information and data in support of the efficacy of sterilization processes in product licence 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)
- Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice (FDA, September 2004)
- Recommendation on the Validation of Aseptic Process (PIC/S, January 2011)
- Guide To Good Manufacturing Practice For Medicinal Products Annexes (PIC/S, September 2009)
- EC Guide to Good Manufacturing Practice (Annex 1) March 2009

2 SCOPE

This guidance document applies to the sterile drug product processed using aseptic processing.

3 GENERAL INFORMATION

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

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

The decision to choose aseptic processing should be justified, for example, due to the instability of a formulation or incompatibility of a pack type.

4 INFORMATION NEEDED FOR ASEPTIC PROCESSES VALIDATION

The following information should be submitted for process validation of drug products manufactured by aseptic processing.

4.1 Premises

It is recommended that a floor plan of the production areas is provided which includes the following information:

- Critical production areas such as: preparation and holding areas, filtering and filling areas, changing rooms and their air cleanliness grade
- Isolators or barrier systems, where applicable
- Location of critical equipment, including, but not limited to, laminar flow hoods, autoclaves, lyophilizers and filling heads

- Material flow and personnel flow

Refer to Annex 4 WHO Good Manufacturing Practices for Sterile Pharmaceutical Products (Technical Report Series No. 957 2010) for the detailed requirement of the grades of clean areas in operation for the manufacture of sterile medicinal products.

4.2 Sterilization and Depyrogenation of Containers, Closures, Equipment and Components

4.2.1 Process Description

A short summary of sterilization and depyrogenation processes for containers, closures, equipment and components should be provided.

4.2.2 Process Validation

a. For heat sterilization or depyrogenation, validation report should be submitted which includes the following information:

- Heat distribution and penetration study summary reports, including, but not limited to, load pattern diagram(s) with identified cold spot(s)
- Biological challenge study report

If the bulk drug solution is aseptically formulated from components that are sterilized separately, validation report of each of the separate sterilization processes should be provided.

For depyrogenation, information on the method of endotoxin challenge used and results showing reduction of endotoxin titer by three of more logs should be presented.

b. For sterilization by irradiation, validation report should be submitted which includes the following information:

- Radiation facility
- Radiation source, method of exposure (i.e. movement through the irradiator)
- Type and location of dosimeters used to monitor routine production loads
- Packaging configuration data
- Multiple-dose mapping studies
- Microbiological methods and controls used to establish, validate and audit the efficacy of the cycle

c. Validation information for sterilization processes other than heat or irradiation should also be provided. Refer to Annex A3 (Section 4.2) for more details.

4.3 Filtration and Holding Time

a. A description of bulk solution filtration process should be provided which includes:

- Filtration processes and specifications
- Tandem filter units, pre-filters and bacterial retentive filters

Pore sizes of 0.2 µm or less are acceptable without further justification. A proposal to use a larger pore size in combination with an additional sterilisation step has to be validated and justified.

Pre-filters and bacterial retentive filters integrity testing information should be provided. Justification should be provided if pre-filtration is not applied.

Information on compatibility and microbial retention capacity of the filters should be provided. Effects of the filter on the drug product formulation should be described, if any.

b. Specifications for holding time between the compounding of the bulk drug product and its filling into final containers should be provided which includes:

- Holding container
- Duration
- Temperature
- Other conditions of storage, if any

4.4 Media Fills

Approach and specification used for media fills as well as the summary of recent media fill results (at least three consecutive separate successful runs), including failures, should be provided.

These data should be obtained using the same filling line(s) that are to be used for the routine production of the finished drug product.

The number of containers filled during the media fills should be in the range of 5000 to 10000 units. For operations with production sizes under 5000 units, the number of media filled units should be at least equal to the maximum batch size made on the processing line.

In general, the following information is recommended to be provided for each media fill run:

a. Date of each media fill
b. Filling room and list of equipment
c. Container-closure type and size
d. Volume and type of medium used in each container
e. Number of units filled, rejected, incubated and positive results observed
f. Incubation information, e.g. duration, temperature and orientation of container
g. Simulations [1]
h. Process parameters [2]
i. Tabulated results and conclusion of microbiological environmental monitoring

Note 1: The procedures used to simulate any steps of a normal production fill should be described. This may include, for example, slower line speed, personnel shift changes, equipment failure and repair, mock lyophilization and substitution of vial headspace gas.

Note 2: The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled or duration of filling) should be compared.

4.5 Container Closure System Integrity

The data, including a short description of method, summary of test results, demonstrating the integrity of microbiological barrier of the container-closure system should be provided.

5 GLOSSARY

Aseptic Processing:
Processing of drug product in grade A or an environment that typically includes sterile filtration and filling steps.

Bioburden:
The total number of all viable aerobic bacteria, yeasts and moulds expressed as colony forming units (CFU) per unit or gram of drug product.

Depyrogenation:
A process used to destroy or remove pyrogens (e.g. endotoxin).

Media fills:
Method of evaluating an aseptic process using a microbial growth medium. Media fills are understood to be synonymous to simulated drug product fills, broth trials and broth fills etc.