Standard Operating Procedure

Title: Guideline for the Validation of Aseptic Processing

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1 PURPOSE

The purpose of this document is to provide a set of guidelines to be used when determining a suitable approach for the qualification of aseptic processing validations at the manufacturing facility involving in aseptically filled medicinal products.

2 SCOPE

These guidelines provide suggestions and considerations for the design and preparation of aseptic media fill validations protocols and reports. They are intended to be used as guidelines only, alternative approaches for validation may be appropriate and can be used provided that the principals of validation as outlined in the company Validation Master Plans are followed.

Out of scope are closed aseptic processing systems where no aseptic connections are made post sterilisation and temperature and pressure are monitored during Steam In Place (SIP) sterilisation.

3 SAFETY

All safety requirements for relevant production areas must be followed at all times.

4 REFERENCES

PICS 2009 Guide to Good Manufacturing Practice for Medicinal Products Annex 1

Current BP <A266> and USP <1211> Monographs

5 INTRODUCTION

The sterility assurance for aseptic processing during final formulation and filling cannot be measured by the sterility test alone and therefore it is critical to routinely challenge the actual aseptic process under “worst case” conditions. Aseptic processing is challenged using microbiological growth media under simulated conditions.

The media fill is a simulation of the entire aseptic formulation and filling process, which substitutes a microbiological growth medium for a sterile product. The media fill also provides a way to evaluate changes made to aseptic processing operations which may affect the sterility assurance of the final product and the performance of aseptic filling personnel under operational conditions.

6 PRE-REQUISITES FOR ASEPTIC PROCESS VALIDATION (MEDIA FILLS)

Before aseptic assembly or processing, different parts of the final product are generally subjected to different sterilisation processes, such as dry heat, moist heat, and sterile filtration.

Each stage of the aseptic filling operation requires validation and control as a pre-requisite to aseptic processing. Each also introduces the possibility of error that might ultimately lead to the distribution of contaminated product. Any manual or mechanical manipulation of the sterilised drug, components, containers, and closures prior to or during aseptic assembly poses a risk of contamination and thus necessitates careful control.

GMP facility ensures that a combination of full equipment qualification, component and equipment protection during handling and storage and rigorous personnel training are essential to the safe manufacture of aseptically manufactured products.

7.4 Facility Shutdowns and Recommissioning

In the event of a filling line shutdown and recommissioning at least one media fill should be conducted prospectively (before commencement of aseptic filling). The results of at least the 7day inspection should be known before aseptic filling of product commences, though approval to fill on risk can be proceeded through the Deviation Procedure.

For major changes to the dispensing facility three consecutive media fills should be conducted to completely requalify the line. (Two of these may be conducted concurrently with manufacture). Any product manufactured before the results of the entire media fill series are known should be quarantined.

7.5 Routine Clean Room Classification

Room classifications are performed to demonstrate that the quality of air within an environment routinely meets the grade required to carry out critical operations. The process of classification involves the sampling of non-viable particulate material to define the size and quantity of particles within the environment. The quality of air within the room is directly related to the composition of non-viable particles and defined as either a room grading under GMP's or an ISO class under ISO 14644:2.

Routine "**in operation**" classification for Grade A and B zones within aseptic filling areas are performed on a 6 monthly basis. During classification the room should be in an "in operation" state as defined in section 6.3 and can be performed during normal operations, media fills or under simulated operations.

For each room the highest classification to achieve is the requirement state in the GMP code for PIC'S products. This provides the maximum permitted airborne particle concentration for 0.5 and 5.0µm particle for each grade as given in the following table:

Table 3 – Non-viable Particles Classification (PIC'S)

Room Classification	PIC'S Code			
	At Rest		In Operation	
	0,5 µm	5.0 µm	0,5 µm	5.0 µm
Grade A	3 520	20	3 520	20
Grade B	3 520	29	352 000	2 900

For the classification purposes, a minimum sample volume of $1m^3$ should be taken per sample location. The minimum number of sample locations has been defined according to EN/ISO 14644-1 for classification purposes and is summarised in Table 4 and in Diagram 1.

Particulate monitoring in the Grade A area should be carried out near the crimping station in filling rooms to demonstrate that the hydraulic crimping does not present a particulate risk to the product.

and must be incubated with the main packs in the same conditions and will be included in the final count of units filled during this process simulation run.

During the filling operation, any unit that lack integrity should be rejected and reason for rejection clearly documented (e.g. pack number, reason for being discarded).

10 SIMULATION CONDITIONS

The design of initial Media Fill must consider all line interventions and include worst case to demonstrate that the manufacturing process is capable of excluding contamination from the sterilised product. The validation may for example include slower line speed, routine interventions, personnel breaks, simulated equipment adjustment, maximum number of processing personnel in attendance, cleaning operations etc.

All planned interventions which would occur during normal filling must be simulated for every fill.

The simulated worst case conditions should be described in the media fill production records.

10.1 Aseptic Processing Operators and Support Personnel

All personnel who are authorised to enter the aseptic processing room during manufacturing, including fill operators, new fill operators under training and maintenance personnel, should participate in a media fill at least once a year. Participation should be consistent with the nature of each operator's duties during routine production. Names of all personnel in attendance should be clearly documented. Maximum two (2) personnel are allowed in each fill room during in-operation conditions. Names of the personnel permitted (qualified) to enter the filling rooms are displayed on Form-840 "List of Permitted Personnel to Enter Filling Clean Rooms" located on the filling suite doors.

10.2 Procedures

Wherever possible, use materials, components and closures that have been stored in the area for the maximum allowed time. Alternatively, provide a reference to the validation of the maximum storage times.

Fill the smallest unit at the fastest speed (handling difficulty).

Fill the largest fill at the slowest operating speed (maximum exposure).

Program the run over the maximum nominated holding and dispensing times allowed. If necessary, suspend filling during the run to ensure the equipment and filter systems are exposed for the maximum time.

Introduce "worst case" manipulations and interventions per the Media Fill SOP and Batch Record Form. Document the planned manipulations and interventions and record the actual activities.

Fill volume should be approximately 50% of the container capacity and all packs and containers should be inverted ensuring that there is sufficient wetting of all internal surfaces of the container / closure.

Note: Ensure that this does not significantly increase the rate of filling and hence minimise the container exposure time.

10.3 Equipment - Maintenance and Breakdown Simulation

Simulate adjustments to equipment expected to be conducted during routine operations.

14 ACCEPTANCE CRITERIA AND RESPONSES

14.1 General Requirements

The target is zero positives. Any positive unit indicates a potential sterility assurance problem, regardless of run size. All positive units should be identified and should result in a thorough, documented investigation. If the positive units are indicative of an unacceptable practice (e.g., an incorrect or inappropriate type of intervention) it should be corrected.

Initial qualification requires a minimum of 3 consecutive successful process simulation tests with no positives on any run. If there are any contaminated units in a single run, investigate the cause; carry out corrective action as appropriate and then repeat the qualification process.

14.2 PIC'S - Acceptance Criteria

Target:

- NIL positives in 5000 units

Limits:

- When filling < 5000 units, no contaminated units should be detected.
  - One (1) positive results in an investigation, halt to production (of European product) and revalidation;
- When filling 5000 to 10 000 units:
  - One (1) contaminated unit should result in an investigation, including consideration of a repeat media fill;
  - Two (2) contaminated units are considered cause for revalidation, following investigation and halt to production (of European product).
- When filling more than 10 000 units:
  - One (1) contaminated unit should result in an investigation;
  - Two (2) contaminated units are considered cause for revalidation, following investigation and halt to production (of European product);

The following table lists the number of positive containers allowed based on the number of units incubated:

Table 1 Acceptance Criteria, Action and Alert Limits

Number Incubated	Target	Alert Level (investigation required)	Action Level (Failure)
<5,000	**0**	**1**	**1**
>5,000	**0**	**1**	**2**
>10,000	**0**	**1**	**2**

14.3 Other - Acceptance Criteria

Target: NIL positives in 5000 units

Limits: When filling 5000 units

- 1 - 5 positive units results in an investigation (alert).
- Six (6) positive units results in an investigation, halt to production and remediation/ revalidation (failure).

The following table lists the number of positive containers allowed based on the number of units incubated:

Table 1 Acceptance Criteria, Action and Alert Limits

