Aseptic Process Simulation

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"The Aseptic Core" discusses scientific and regulatory aspects of aseptic processing, with an emphasis on aseptic formulation and filling. This column has been developed with the intention of providing practical advice to professionals involved in the qualification of aseptic processes and the myriad support processes involved. The primary objective for this column: Useful information.

Reader comments, questions, and suggestions are needed to help us meet our objective for this column. Suggestions for future discussion topics are welcomed. Discussion topics and case studies related to aseptic processing submitted by readers are invited. Please email your suggestions to shaigney@advanstar.com.

KEY POINTS

The following key points are discussed in this article:

- Aseptic process simulation (media fills) is the lynchpin of any qualification of an aseptic facility
- Aseptic process simulations should be carefully planned to ensure the length of the simulation and the number of manipulations performed during the fill are representative of the actual process
- A matrix or bracketing approach may be taken for a facility or filling line where multiple products or dosage forms are filled or processed
- For a new facility or process, it is advisable to perform a few practice fills before performing an aseptic process simulation
- Aseptic process simulations need their own batch records that mimic the process being simulated and include details such as number and type of aseptic manipulations, number of personnel, length of run, line speed, etc.
- The growth medium used for aseptic process simulations is typically soybean casein digest medium (SCDM), although other media may be used with suitable growth promotion.

INTRODUCTION

Aseptic process simulation is one of the last steps in qualification of an aseptic processing facility (typically just prior to conformance runs). Aseptic process simulations are also a key element of ongoing process validation of an operational aseptic processing facility.

This article briefly discusses the definition of an aseptic process simulation; describes how to set up an aseptic process simulation program; gives some points to consider, and provides typical examples.

WHAT IS ASEPTIC PROCESS SIMULATION?

Aseptic process simulation is a method to determine if a purportedly aseptic process really is aseptic. In an aseptic process simulation, the aseptic process (or a portion of the aseptic process) is performed using growth media instead of the products or chemicals in the process being simulated. The growth media from the simulation is then sterility tested. If it is sterile, it can be assumed that the process was performed aseptically. If not, then the source of the contamination should be investigated, corrective and preventive actions should be made, and the aseptic process simulation should be repeated.

Media Fills

The most common aseptic process simulation is the media fill. In a media fill, a representative number of dosage units, typically >5,000 units, are filled, sealed, and placed in one or more incubators where they are incubated for 14 days at the proper temperature(s) to promote microbial growth (typically 7 days at 20–25°C, followed by 7 days at 30–35°C). The filled units are then inspected for microbial growth.

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If all units are negative for growth, a growth promotion study is performed on the media. If the growth promotion passes, the media fill is successful. If the growth promotion study fails, the failure must be investigated and the media fill repeated. If there are positive units in the media fill vials, the source of the contamination must be investigated, corrective and preventive actions made, and the media fills repeated.

Other Aseptic Process Simulations

Some of the other processes where aseptic process simulation may be performed include the following:

- Aseptic compounding
- Aseptic crystallization
- Aseptic precipitation
- Bioreactor and fermenter charge and inoculation
- Other aseptic processes in the biotech and parenteral industries.

Each of these processes has unique requirements that make performing an aseptic process simulation useful.

SETTING UP AN ASEPTIC PROCESS SIMULATION PROGRAM

Aseptic process simulation should be part of the overall process validation program for a new facility. This program should be part of the facility master plan or a separate aseptic processing procedure. Steps to setting up an aseptic process simulation program include the following:

- **Defining the aseptic processes.** Review your manufacturing processes to determine the number of aseptic processes and the number of aseptic unit operations.
- **Performing a risk assessment on each aseptic process.** Perform a high level risk assessment for each aseptic process to determine its effect on patient safety and product quality. Separate the processes that could result in a non-sterile product, such as filling of a final product, from processes that may cause loss of product but little or no risk to patients, such as addition of growth factors or nutrients to a bioreactor.
- **Evaluating each process for key control points and key factors that could present a risk of microbial contamination of the product.** Items to consider include the following:
  - Length of the process
  - Number of people involved in the process
  - Shift changes or breaks involved in the process
  - Line speeds (if applicable)
  - Line configuration
  - Operator interventions in the process (e.g., removal of tipped vials from a filling line, weight checks, manual addition of a sterilized powder to a sterile suspension formulation, aseptic sampling, etc.)
  - Any special conditions, such as lyophilization, product recirculation for suspensions, etc.
- **Determining the frequency and number of runs for each aseptic process simulation.** Some aseptic process simulations may be performed only as a verification activity during commissioning of new equipment, such as bioreactors or fermenters. Most aseptic process simulations, however, will be performed on a routine, usually semi-annual basis. During initial qualification during start-up of a facility, you will perform three media fills before proceeding to the process validation or conformance lot phase of the start-up.

  Something that should be considered during this stage is if you are going to use a bracketing or matrix approach for your aseptic process simulation program. For an aseptic filling process, for example, you would rotate factors such as line speeds, vial sizes, lyophilized products, and other processes that might prove "worse case." Processes that are not worse case, such as an intermediate vial size between largest and smallest vial might be covered by media fills for the largest and smallest vials in the routine manufacturing schedule.
- **Developing batch records or process instructions for each aseptic process simulation.** Each aseptic process simulation needs detailed instructions on how to perform it. This is usually accomplished by a specialized batch record or manufacturing instruction for the aseptic process. A good aseptic batch record will include the number and type of aseptic manipulations observed in the manufacturing process, line speeds, duration of runs, the number of people in the aseptic processing area for each run, environmental monitoring during the run, growth media used for process simulation, incubation times, and temperature, etc.
- **Developing a schedule for aseptic process simulations.** Aseptic simulations are required on a semi-annual basis for critical aseptic processes such as aseptic filling. These should be included in the routine production schedule so

that they are considered part of the routine manufacturing process. When scheduling an aseptic process simulation, ensure that factors such as line speed, vial size, aseptic manipulations, etc., are scheduled into the aseptic process simulation so that any bracketing or matrix approach is covered on a routine basis.

PERFORMING AN ASEPTIC PROCESS SIMULATION

An aseptic process simulation should simulate the original process as closely as possible, given the obvious constraints imposed by the use of media instead of actual product for the simulation.

The first step in an aseptic process simulation is preparing the growth media. This is typically soybean casein digest medium (SCDM), although other media such as fluid thioglycollate broth, peptone broth, etc., may be used in special cases. In any case, you will have to perform growth promotion studies on your growth media with your environmental isolates as well as standard growth promotion organisms. This media is used for the remainder of the simulation to represent the product being processed. The media is typically compounded, then sterilized by sterile filtration or moist heat sterilization, as applicable.

Equipment used in the aseptic process simulation should be sterilized or sanitized as in the normal process; all ancillary items should also be sterilized or sanitized per the normal process.

Once the media, equipment, and ancillary items are prepared, the operators perform the process simulation as closely as possible to the original process, including the aseptic techniques, routine manipulations, number of personnel, line speeds, length of run, etc.

The media-containing vials, ampoules, syringes, etc. or bulk media are collected and incubated for 14 days at an appropriate temperature (typically 7 days at 20-25°C and 7 days at 30–35°C). If there is no growth, the media are tested for growth promotion using standard test organisms plus routine environmental organisms. On successful growth promotion, the aseptic process simulation can be considered successful.

ASEPTIC PROCESS SIMULATION EXAMPLES

The following sections highlight some examples of aseptic process simulation.

High Speed Filling Line

Key items to consider for a high-speed filling line are the run size and run length. A high-speed filling line may run 200,000 vials over two shifts. Running 5,000 vials over a 10- to 20-minute period is not representative of the process. Consider increasing the run size to something more representative of the process. Also, increase the run length to the actual run length by running the line in short bursts followed by lengthy downtimes. For example, for a two-shift operation running 200,000 vials a day, you might fill 5,000 vials at the beginning of the run, 5,000 vials before shift change, 5,000 vials after shift change, and 5,000 vials at the end of the day, for a total of 20,000 vials. Typical aseptic manipulations such as removing tipped vials, weight checks, line clearance, etc., would be included throughout the 20,000 vial fill.

Lyophilized Product

A lyophilized product fill will typically be smaller, due to lyophilizer capacity. A 5,000-vial fill is probably a sufficient size for a media fill. For a lyophilizer fill, you would simulate a normal filling process, including partial insertion of the stoppers, and load the vials onto lyophilizer shelves maintained at room temperature (20–25°C). When all of the vials are filled, the lyophilizer would be sealed, and a partial vacuum would be pulled on the lyophilizer. The vacuum would then be released, and the normal transfer and capping processes would be simulated. Routine considerations such as number of aseptic manipulations, shift changes, line speeds, etc. should be included in an aseptic process simulation for a lyophilized product.

Low Speed Filling Process

One of the considerations in a low speed filling process is that the run size may be less than 5,000 units. If feasible, I recommend performing a 5,000 unit fill. If not practical, fill the maximum batch size. You should have a rationale for filling less than 5,000 units built into your media fill procedure, explaining the reason for the smaller size fills and any mitigating actions. It is important to have a justification in writing, as the regulatory agencies will ask about your media fill run size.

Bioreactors And Fermenters

This type of aseptic process simulation is usually only performed during commissioning of a new bioreactor or fermenter, or if a major change is made to a bioreac-

tor or fermenter. This type of aseptic process simulation is not required in any regulation or guideline that I am aware of, but I consider it a good practice before committing the bioreactor to processing product. In this simulation, you perform the operations such as transfer of the contents of a seed bioreactor to the main bioreactor, aseptic sampling of the bioreactor, transfer of growth factors or media, transfer of the cell broth to a harvest tank, etc. The media is incubated for a 14-day period and then tested for sterility. In some cases, the entire media batch may be filtered and the filter tested for sterility per routine sterility test procedures. Because this is usually a commissioning and verification test, there is more leeway in how the test is performed than with aseptic simulation of filling processes. In any case, the objective of this simulation (i.e., final shakedown before committing product, diagnostic for fermenter and bioreactor contamination investigation, etc.) should be carefully considered when you are designing the process simulation.

VALIDATION IMPLICATIONS

Aseptic process simulation is a critical validation procedure that is performed before implementing a new aseptically-manufactured product or aseptic process. Careful consideration and design of an aseptic process simulation is required for successful implementation.

GENERAL REFERENCES

FDA, *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice*, 2004.

European Commission, Enterprise and Industry Directorate-General. *EudraLex–The Rules Governing Medicinal Products in the European Union–Volume 4*–EU Guidelines to Good Manufacturing Practice–Medicinal Products for Human and Veterinary Use, Annex 1: Manufacture of Sterile Medicinal Products (corrected version), 2008. **JVT**