

Technical Report No. 22
(Revised 2011)
Process Simulation for
Aseptically Filled Products



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Process Simulation for Aseptically Filled Products PDA Task Force

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1.0 Introduction

This document replaces the original PDA *Technical Report No. 22, Process Simulation Testing for Aseptically Filled Products*, published in 1996. The intent of the current effort is to update that document to reflect the continuing changes that have occurred in aseptic processing technology within the global industry. We have attempted to address the subject as fully as possible recognizing the notable contributions by other organizations, regulators, compendia and individuals who have worked in this area. In addition the report provides guidance where risk based approaches may be applied.

This technical report was disseminated in draft for public review and comment prior to publication. Many of the submitted comments have been included in the final document. We believe this approach accomplished the widest possible review of the document and ensures its suitability as a valuable guide to industry in the area of process simulation for aseptic processing operations.

This technical report should be considered as a guide; it is not intended to establish any mandatory or implied standard. The reader must recognize that there may be additional requirements imposed because of new or localized regulatory expectations that are not included in this document. This technical report does not provide a universally appropriate template for the execution of process simulation studies. Each company must determine the appropriate rationale and approaches applicable to their unique operations.

A recurring theme in this report is the consideration of risk to product sterility and patient safety as criteria for the design of the aseptic process simulation studies. Regulatory authorities have issued recommendations for aseptic process study design and companies should be aware of these recommendations when planning their studies. However, the use of relative risk and scientific evaluation as a means to provide information used to make decisions on study design may be of benefit because it should result in better understanding of the aseptic process and its capabilities. The use of risk assessments and related information may result in studies which go beyond the recommendations of regulatory authorities. It may also result in studies which differ from those recommendations. However, it should not result in studies which are less effective than those recommended by regulatory authorities.

1.1 Scope

This technical report addresses process capability assessment for aseptic processing. Such assessments consist of one or more aseptic process simulations (APS) during pharmaceutical and biopharmaceutical formulation and filling activities (referred to as secondary manufacturing in many parts of the world). Aseptic operations required in the preparation of sterile bulk materials and biotechnology inoculums, and feed materials are not a part of this document; refer to PDA *Technical Report No. 28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals (1)*.

While the focus of this document is on aseptic processing in the pharmaceutical and biopharmaceutical industry, application of the concepts and principles to the preparation of sterile medical devices and diagnostics may be appropriate.

1.2 Previous PDA Publications

PDA has published previous reports on the aseptic filling process: *Technical Monograph No. 2: Validation of Aseptic Filling for Solution Drug Products*; *Technical Report No. 6: Validation of Aseptic Drug Powder Filling Processes*, and the 1996 edition of this report, *Technical Report No. 22: Process Simulation Testing for Aseptically Filled Products (2,3,4)*.

1.3 Reason for Revision

Since the above reports were issued, there have been continued advances in facility and equipment design, such as the use of barrier, isolation and blow-fill-seal technologies. The understanding and philosophies of aseptic process qualification, validation and control have evolved as well. In addition, global regulatory and standards authorities have revised their own guidance's on aseptic processing (5,6,7,8).

The 2011 version of Technical Report No. 22 features the following new or revised information.

- Risk Management: This report frequently references the use of quality risk management concepts in the design of APS programs
- Concepts and Principles: There have been clarifications and enhancements of **Section 3.0**, in keeping with current scientific knowledge, experience and regulatory expectations
- Lyophilized Products: The section on “Lyophilization of Dilute Medium” has been removed as this APS approach is generally not considered appropriate.
- Freezing of Media: For similar reasons references to freezing of media have been removed.
- Powder Filling: Certain APS approaches for powder filling have been removed, including:
 - On-line powder fill followed by off-line liquid fill
 - Non-aseptic liquid fill, sterilized, and followed by on-line powder fill
 - Off-line liquid fill followed by on-line powder fill
- Isolators, restricted access barrier systems (RABS), blow-fill-seal (BFS): Updated information include in **Section 4.8**
- Elements of APS: Enhanced information is included for: filling speed, interventions, and duration and number of units filled
- Interventions: This report differentiates aseptic process interventions as either “inherent” or “corrective,” a distinction that is helpful in understanding their relationship to microbial contamination and the design of the APS program.
- Acceptance Criteria: Section 10 includes background, current recommendations and good practices in setting acceptance criteria for the APS
- On-going Process Evaluation: Formerly referred to as ‘Validation Maintenance,’ this section has been updated to reflect that the state of control is an ongoing process.

Note: This 2011 revision of Technical Report No. 22 represents a significant update of the content of the report. This version should be treated as a full replacement of the 1996 version. As such, readers/users should fully review this edition. With the publication of the 2011 version of Technical Report No. 22, PDA no longer supports or considers valid the 1996 version.

1.4 Purpose

Aseptic process simulation (sometimes referred to as a media fill) is a useful tool to evaluate the capability of aseptic processing activities. For the results to be meaningful, engineering and manufacturing controls, maintenance activities, quality systems, employee training, written procedures, environmental control, environmental monitoring, strict adherence to aseptic technique, and intervention controls should be in place. APS simulates the aseptic process from the point of product and component sterilization to closure of the container (including any process/handling

steps subsequent to sealing that might impact container integrity), substituting a microbiological growth medium for the sterile product.

The aseptic process simulation also provides a means for the evaluation of changes made to an aseptic processing operation which might impact the sterility of the final product. An aseptic process simulation can be useful in identifying potential weaknesses in an aseptic process that might contribute to the microbiological contamination of the product during processing.

The purpose of an aseptic process simulation is to:

- Assess the capability of an aseptic process under a given manufacturing environment and process controls
- Demonstrate that appropriately designed and implemented process changes are acceptable
- Evaluate the proficiency of aseptic processing personnel
- Demonstrate compliance with current Good Manufacturing Practice
- Demonstrate the appropriateness of operating practices used in support of aseptic processing
- Challenge the aseptic process for microbial contamination vulnerabilities

The successful completion of an APS cannot be considered a validation of aseptic processing in the same sense that a performance qualification effort involving biological challenge and temperature measurement can support a steam sterilization process. Aseptic processing relies heavily on personnel intervention practices, equipment features, facility design/control and procedures that in combination serve to exclude microorganisms from sterile components and products. These elements of aseptic processing cannot be as rigorously controlled as a sterilization process; resulting in a higher risk of contamination. The aseptic process simulation is only a demonstration of the capability of the process to produce sterile products aseptically at the time of its execution using the defined process, materials, facility, equipment and personnel.

The APS does not provide information which relates directly to the sterility of a specific product batch. Therefore, the fact that a specific APS does not meet the required acceptance criteria does not necessarily indicate a sterility problem for any particular production batch. However it is an indication that some event has occurred during the APS leading to contamination of one or more units. The potential impact of the event on production materials must be determined.

Similarly, the successful performance of a high-risk aseptic intervention, technique or practice in a simulation does not in itself justify its use or acceptability during production. The aseptic process simulation is one tool for evaluating the processing steps used to manufacture a sterile product. The APS provides supporting data demonstrating the on-going capability of producing sterile product by aseptic processing

A holistic approach must be used to control aseptic processes. An aseptic process incorporates many systems to assure and control sterility of the materials produced. These systems include:

- Product, equipment and component sterilization
- Personnel training and certification of aseptic gowning and aseptic techniques
- Equipment and facility sanitization programs
- Environmental system: microbial levels, differential pressure, air pattern, velocity, temperature and humidity, air supply
- Personnel, material and equipment flows

- Standard operating procedures/ work instructions or their equivalent.
- A underlying quality system approach to process control

These systems must be routinely monitored to provide verification of their continued acceptable performance, by which the sterility assurance of a manufactured product can be established. Therefore, it is important to validate all of the related sanitization and sterilization processes independently, such as sterilization/ depyrogenation of the product, container, closure and all product contact and indirect product contact surfaces (e.g., stoppers, hoppers).

2.0 Glossary of Terms

Action Level (environmental monitoring)

An established microbial or non-viable particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

Action Plan

A written plan consisting of elements to be accomplished to achieve a specific result. The plan describes responsibility for each element and a target date for completion.

Aerobic microorganism

A microorganism that utilizes oxygen as the final electron acceptor during metabolism; a microorganism that will grow primarily in the presence of oxygen. For the purpose of this report, this definition encompasses facultative anaerobes.

Alert Level (environmental monitoring)

Established microbial or non-viable particle level giving early warning of potential drift from normal operating conditions; not necessarily grounds for definitive corrective action but typically requires follow-up investigation.

Anaerobic organism

A microorganism that does not utilize oxygen as the final electron acceptor during metabolism; microorganism that will grow only in the absence of oxygen.

Aseptic Filling

The part of aseptic processing where a pre-sterilized product is filled and/or packaged into sterile containers and closed.

Aseptic Processing

Handling sterile materials in a controlled environment, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

Aseptic Processing Area (APA)

Controlled environment, consisting of several zones, in which the air supply, facility, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

Aseptic Processing Simulation (APS)

A means for establishing the capability of an aseptic process as performed using a growth medium.

Note: Aseptic processing simulations are understood to be synonymous with media fills, process simulations, simulated product fills, broth trials, broth fills, etc.

Barrier System

A system of physical partitions that affords ISO 5 protection by partially separating its interior from the surrounding environment utilizing airflow.

Bioburden

Total number of viable microorganisms on or in a health care product prior to sterilization.

Campaign

A series of consecutive production batches manufactured without intervening cleaning and sterilization.

Change Control

A formal program that describes evaluation and actions to be taken if a change is proposed or completed to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or a proposed or completed change that may affect the operation of the quality or support systems.

Colony Forming unit (CFU)

One or more microorganisms that produce a visible, discrete growth entity on a semi-solid, agar-based microbiological medium.

Compounding

A process in which a bulk drug substance is combined with one or more excipients and/or another bulk drug substance to produce a drug product.

Contamination Rate

The percentage of units filled in a process simulation that are positive for microbial growth after incubation.

Critical Area

An area designed to maintain sterility of sterile materials. Sterilized product, containers, closures, and equipment may be exposed in critical areas

EnvironmEntal Flora (isolatEs)

Microorganisms associated with a processing environment.

EnvironmEntal monitoring Program

Defined, documented program which describes the routine particulate and microbiological monitoring of processing and manufacturing areas. (**Note:** The program should reference a corrective action plan in cases where action levels are exceeded.)

Growth Promotion TEst

Test performed to demonstrate that media will support microbial growth.

IntEgrity TEst

Test to determine the functional performance of a membrane filter or container/closure system.

IntErvention

An aseptic manipulation or activity performed by personnel that occurs within the critical area. This technical report regards interventions as either corrective or inherent.

IntErvention, CorrEctivE

An intervention that is performed to correct or adjust an aseptic process during its execution. Examples include such activities as: clearing component misfeed, adjusting sensors, and replacing equipment components.

IntErvention, InhErEnt

An intervention that is an integral part of the aseptic process and is required for set-up or routine operation and/or monitoring, e.g., aseptic assembly, container replenishment, environmental sampling, etc. Inherent interventions are required by batch record, procedure, or work instruction for the proper conduct of the aseptic process.

ISo 5

Environmental operating conditions defined in ISO 14644-1, "Cleanrooms and associated controlled environments" (5). (**Note:** For total particulates, ISO 5 approximates the Class 100 description from the now obsolete U.S. Federal Standard 209, and is roughly comparable to Grade A as defined in European GMP Annex 1 – "Manufacture of Sterile Medicinal Products.")

Isolator, ClosEd

A decontaminated unit meeting ISO 5 conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment. Any air exchange with the surrounding environment takes place only through microbially retentive filters.

Isolator, opEn

A decontaminated unit meeting ISO 5 conditions that provides uncompromised, continuous, isolation of its interior from the surrounding environment. It may transfer air directly to the surrounding environment through openings (e.g., "mouse holes") that preclude the ingress of microbial contamination.

mEdia Fill

See Aseptic Processing Simulation.

microbiological IdEntification

Biochemical characterization of isolated colonies to determine the isolate genus and, where feasible and appropriate, the species.

PositivE unit

Unit filled in an aseptic process simulation that exhibits detectable microbial growth after incubation.

REstrictEd AccEss barriEr SystEm (RABs)

RABS are aseptic processing systems (ISO 5) intended to substantially reduce human borne contamination within the aseptic environment where sterile product, containers, closures and equipment are exposed by the use of separative devices and defined mechanical features and operating procedures.

Shift

Scheduled periods of work or production, usually less than 12 hours in length, staffed by alternating groups of workers.

Sampling FrEquency

Established period for collecting samples.

StErilE

Absence of life; usually refers to absence of viable microorganisms.

Note: In practice, no such absolute statement

regarding the absence of microorganisms can be proven (see sterilization).

Sterility Test

Test performed to determine if viable microorganisms are present.

Sterilization

Validated process used to render a product free of viable microorganisms.

Note: In a sterilization process, the nature of microbiological death or reduction is described by an exponential function. Therefore, the number of microorganisms which survive a sterilization process can be expressed in terms of probability. While the probability may be reduced to a very low number, it can never be reduced to zero.

Validation

Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. (**Note:** There has been wide-spread evolution in the concept and definition of validation in recent years. Readers should refer to the U.S. FDA, EC and other related regulatory definitions and guidance regarding validation.)

Worst Case

A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

3.0 Process Simulation Concepts and Principles

The validation of an aseptic processing operation should include aseptic process simulations using a microbiological growth medium in place of the product. This aseptic process simulation, or media fill, normally includes exposing the microbiological growth medium to product contact surfaces of equipment, container closure systems, critical environments, and process interventions to closely simulate the same exposure that the product itself will undergo. Results are then interpreted to demonstrate the potential for a unit of drug product to become contaminated during actual operations.

3.1 Number and Frequency of Simulations

The number and type of aseptic process simulations performed should be based on an assessment of risks posed by the process or significant changes to the process. New facilities and processes are regarded differently based on the determination of those risks.

For a new facility or production process, process simulations are performed as part of the overall validation activities. Initial process simulations are generally conducted after completion of:

- Equipment qualification
- Facility environmental system qualification
- Sterilization process validation
- Implementation of environmental decontamination procedures
- Personnel training and gowning certification
- Environmental monitoring
- Room qualification
- Standard operating procedures

The aseptic process simulation supports that a new facility, line or process is operating under the desired state of control. Historically, there has been a regulatory expectation that at least three consecutive successful process simulations are performed when qualifying a new facility, filling line or process (6,7,8). This may be an appropriate activity to utilize risk management approaches.

There is a regulatory expectation for at least semi-annual simulations for a qualified facility, line or process (6,7,8,9). Additional process simulations may be required based on a risk assessment to assist in the evaluation of any major changes to procedures, practices or equipment configuration (See **Section 12.0 – Ongoing Process Evaluation**). Flexibility in media fill design may be appropriate for isolators which offer robust separation (built in by design) and a consistently heightened level of product protection.

3.2 Worst Case

A useful technique in the validation of pharmaceutical processes is the employment of “worst case” scenarios. The use of “worst case” situations is intended to challenge the process under conditions that may be on the edge of normal operating conditions. If, under the circumstances of the worst case challenge, acceptable results are achieved, then there is greater confidence in the reliability of the system under more routine conditions. Worst case does not mean creation of artificial conditions or environments which exceed allowed operating conditions and which can force a system failure.

Worst case conditions vary depending on the operations or risk being considered. For example, executing the APS using the maximum number of personnel may be worst case at certain times as gowned personnel are the greatest source of microbial contamination in an aseptic process. In other situations worst case may include executing the process with fewer people if this results in more movement by the process operators.

Other examples of “worst case” practices may include:

- Using room/equipment at the maximum time period after completion of sanitization/sterilization (clean hold time)
- Using the slowest fill speed for the largest container (maximum opening)
- Using the highest fill speed for the smallest container (handling difficulty)

The worst case conditions selected for inclusion in an APS should be predefined based upon characteristics of the operation. The identification of appropriate worst case conditions should be accomplished by conducting an assessment of the APS covering the relevant variables and their microbiological impact on the process. Such assessments can benefit from the application of risk management principles. The assessment conclusion should outline the variables selected as worst case and considerations/rationale for their selection.

3.3 Risk Assessment

Risk is defined as the combination of the impact of a hazard or unwanted event and its likelihood of occurring and harming the patient (10,11). The hazard associated with aseptic processing in the context of this technical report is the loss of sterility assurance or potential for pyrogens. The use of risk assessment principles should be of benefit in making decisions related to aseptic processing and its simulation. It would be beneficial to take into account risk to product quality and patient safety when confirming the design of the APS study.

A number of risk assessment methods specific for aseptic processing have been defined (12,13,14,15,16,17,18). A risk assessment may be performed to determine, identify, and evaluate the aseptic process steps and interventions that can potentially adversely affect the sterility assurance risk to the product. Risk assessments can also be used to determine the worst case manufacturing scenarios related to container size, configuration, line speed, batch size, and operating conditions. Where feasible, efforts should be made to mitigate identified risk by eliminating or changing risky process steps, and improving facility, equipment, and process design. The risk assessment should be documented and communicated to stakeholders and management in the organization including the Quality Unit.

3.4 Ongoing Evaluation

An assessment of ongoing controls and changes to the aseptic process, personnel, equipment, computerized systems, facility and critical utilities may be performed to determine the risk of such changes to the assurance of sterility. This assessment may be used to justify the type of response or simulation of the process change needed to assure that the change has not adversely affected the aseptic process. Risk assessment may be beneficial to present a rationale for the need and extent of aseptic process simulation as a result of change control. The risk assessment and risk management decisions should be recorded, approved and incorporated into the change control documentation.

4.0 Process Simulation For Sterile Dosage Forms

The conduct of process simulations for aseptically produced parenteral products entails simulation of the process from the point of sterilization of the product and product contact surfaces, including containers and closures, through sealing of the filled container. Any aseptic activities performed during dosage form compounding are a necessary part of the APS. The following section summarizes considerations to be made in the design and performance of process simulations for aseptically produced solutions, lyophilized products, suspensions, ointments and powders.

The aseptic process is simulated through the use of production operations in which a sterile medium and/or placebo is handled in a manner which approximates as closely as possible the methods used in routine production. The application of this principle to a specific aseptic process or procedure may require adaptation of the methods described in this report to that process or procedure. Such adaptations should be accomplished in a manner which will not reduce the effective challenge of the simulation and, as a result, appear to improve the results of the simulation relative to routine production operations.

It is important to note that where media is utilized in the process simulation its sterilization need not be performed in a manner identical to that utilized for the product being simulated (See **Appendix 13.2**). For example, aseptic process simulations do not support the filtration validation of the product/process being simulated, so differences in the filter area, filter media, etc., are acceptable providing these changes do not enhance the aseptic process or eliminate a process step which could adversely affect the sterility assurance of the product.

This document does not provide a universally appropriate template for the execution of process simulation studies. The following are general approaches to common aseptic processing simulations. Unique product configurations, presentations, and processes may require modification from the information provided in this section. A company must determine appropriate rationale and approaches applicable to their unique operations.

The steps in the execution of an aseptic process simulation are listed in **Appendix 13.3**.

4.1 Aseptic Compounding Activities

The aseptic compounding process simulation may be performed as a stand-alone activity or be fully integrated with the aseptic filling process. Where a separate simulation is performed the methods, practices and acceptance criteria described in *PDA Technical Report No. 28: Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals* may be appropriate (1). When integrated with the filling process no adjustment for the compounding is made in the acceptance criteria.

Process simulation studies should assess all aseptic operations performed subsequent to the sterilization of the materials utilized in the process:

1. Aseptic steps for products that are solutions may be limited to set-up, sampling, and in-situ filter integrity testing.
2. Suspensions, ointments and other non-filterable formulations may require a substantial number of aseptic steps (e.g., sterile powder addition).
3. Processes requiring the addition of sterile powders should employ an acceptable placebo material in containers identical to those utilized in the process being evaluated (See Appendix 13.1).
4. Blending, milling and subdivision processes performed at a sterile powder facility require similar attention.