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Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals

Joint PDA/PhRMA Sterile Bulk Pharmaceutical Chemicals Task Force

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Process Simulation
Testing for Sterile Bulk Pharmaceutical Chemicals

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PDA
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PREFACE—2nd Edition

This document provides guidance relative to the validation of aseptic processing activities associated with the production of sterile bulk pharmaceutical chemicals. It draws upon the concepts and principles developed in PDA's and PhRMA's prior publications on aseptic processing technology (1, 2, 3). This effort expands upon those documents to provide assistance for individuals and firms producing sterile bulk pharmaceutical chemicals. Our goal in this revision was to update the document to reflect 6 years of industry experience with it, as well as an acknowledgement of acceptance criteria limitations that were present in the first edition (4). We have also endeavored to address some of the issues raised by FDA in their review of the earlier edition.

The preparation of sterile materials in the quantity and scale used in the manufacture of bulk pharmaceutical chemicals generally requires equipment and procedures quite different from those used in the manufacture of finished pharmaceuticals. The uniqueness of the production methods for sterile bulks precludes the direct extrapolation of the process simulation approaches employed for aseptically produced sterile formulations.

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 testing for sterile bulk pharmaceutical chemicals.

This document should be considered as a guide; it is not intended to establish any mandatory or implied standard.


Karl L. Hofmann—Bristol-Myers Squibb Co.

Co-Chairmen, Joint PDA/PhRMA Task Force on Sterile Bulk Pharmaceutical Chemicals
1. INTRODUCTION

1.1. Purpose

The preparation of sterile bulk pharmaceutical chemicals requires the combination of classical chemical/biological production methods with the well-defined concepts for the preparation of sterile materials. The integration of these fields entails process equipment and operating procedures which are often substantially different from ordinary practice in either discipline. This document outlines process simulation practices for sterile bulk pharmaceutical chemicals (sterile BPCs), utilizing concepts drawn from both bulk pharmaceutical chemical operations and sterile product manufacturing and adapted to fit the unique nature of these materials. It presents options for determining the adequacy of aseptic operations performed during large scale manufacturing while allowing for realistic acceptance criteria for such operations.

The aseptic procedures utilized in the production of sterile BPCs can be evaluated using a process simulation methodology. However, in certain instances the use of a microbiological growth medium in a bulk manufacturing plant can pose significant problems. It is often necessary to consider other simulation options which pose less potential risk to the manufacturing area. It is useful to utilize a narrower definition of a process simulation in these cases. The following definitions make a clear distinction between possible methods:

1. Process Simulation (without microbiological growth media)

Method of evaluating an aseptic process employing methods which closely approximate those used for sterile materials using an appropriate placebo material.

2. Process Simulation (with microbiological growth media)

Method of evaluating an aseptic process using a microbial growth medium employing methods which closely approximate those used for sterile materials.

The process simulation test also provides a way to evaluate changes made to an aseptic processing operation which might affect the sterility of the final product. It can be useful in identifying potential weaknesses in an aseptic processing operation which might contribute to the microbiological contamination of the product.

1.2. Sterile Bulk Pharmaceutical Chemicals

For the purposes of this document, a sterile bulk pharmaceutical chemical is defined as a sterile material derived from chemical, fermentation or semi-synthetic sources which is final packaged or stored in bulk form. The bulk material may be an active pharmaceutical ingredient (API) or an excipient. Sterile BPCs are typically solids, but may be solutions or suspensions.

1.3. Scope

This document addresses the validation of aseptic processing during sterile bulk manufacturing activities (referred to as primary manufacturing in many parts of the world). It describes methods and procedures for the conduct of process simulation tests, including crystallization, separation, purification, drying, milling, blending and bulk packaging of sterile bulk pharmaceutical chemicals which are aseptically produced. Aseptic operations required in the preparation of sterile formulations are not a part of this document and have been addressed by PDA elsewhere (4).

1.4. Sterile BPC Production Technology

The preparation of sterile bulk materials entails the completion of a series of unit operations under aseptic conditions. The equipment utilized for these aseptic unit operations is sterilized using a validated procedure prior to the introduction of the sterile BPC. Depending upon the process, the equipment may be classified as either a "closed" or an "open" system (see below). While it is recognized that a "closed" system is generally preferred, there are process and equipment limitations such that "open" systems are the only means available for the execution of certain unit operations. The process train for a sterile BPC may include both "open" and "closed" portions. The test methods used for the process simulation must include all portions of the system whether "open" or "closed" and transitions between them (see Section 3).

1.4.1. Closed Systems

A "closed" system is one that is designed to prevent the ingress of micro-organisms by means of physical...
separation from the surrounding environment. A "closed" system:

- Is constructed, installed and qualified in a manner which demonstrates integrity is maintained throughout the full range of operating conditions, and over a time period inclusive of the longest expected usage (i.e., manufacturing campaign). The qualification is done according to a formal protocol, following generally accepted engineering principles, and is documented.

- Is sterilized-in-place or sterilized while closed prior to use using a validated procedure.

- Can be utilized for its intended purpose without breach to the integrity of the system.

- Can be adapted for fluid transfers in and/or out while maintaining asepsis.

- Is connectable to other closed systems while maintaining integrity of all closed systems (e.g., Rapid Transfer Port, steamed connection, etc.).

- Is safeguarded from any loss of integrity by scheduled preventive maintenance.

- Utilizes sterilizing filters for sterilization of process streams which are integrity tested and traceable to each product lot.

By virtue of their design, closed systems provide a substantially increased measure of protection to the materials processed within. Where a sterile BPC can be processed in its entirety within closed systems, the risk of contamination is negligible.

1.4.2. Open Systems

An "open" system lacks one or more of the features of a "closed" system.

1.5. Considerations

A holistic approach must be used to adequately validate and control aseptic processes. A process simulation test is only a point-in-time representation of the capabilities of an aseptic processing system, including environment, equipment, procedures and personnel. It does not ensure that sterile bulk materials produced at other times will have the same level of microbiological quality. However, through control and validation of related processes, such as environmental monitoring, qualification of personnel and validation of cleaning and sterilization cycles, it is possible to maintain the level of asepsis demonstrated during the process simulation test. Therefore, it is important to validate the related sanitization and sterilization processes independently, such as sterilization/depyrogenation of the product, sterilization of the process equipment including product contact surfaces, sterilization of containers (intermediate and final packaged bulk), and support systems such as air, water, or nitrogen (6, 7, 8).

Confidence in the sterility of a specific production lot is gathered through a number of process controls and procedures including: documented and validated sterilization/sanitization procedures, in-process controls regulating the production process, environmental monitoring, comprehensive batch records, extensive qualification of process equipment, and training of operating personnel.

2. PROCESS SIMULATION CONCEPTS AND PRINCIPLES

2.1. Number and Frequency of Tests

For a new facility or production process, process simulations can be performed as part of the overall validation. Initial process simulation tests, if performed, are conducted after equipment qualification, sterilization process validation, and personnel training have been performed, and environmental monitoring has demonstrated that the new facility is under the desired state of control (9, 10, 11). If a process simulation test fails in the absence of this supportive work, identification of a possible root cause will usually be more difficult. Three consecutive successful process simulation tests are performed when evaluating a new facility or process. Prior to release of the new facility, or new process for production use, acceptable results from these process simulation tests should be achieved to demonstrate the reproducibility of the process. In existing facilities, a process simulation test program should be considered for each aseptic process. Additional process simulation tests may be considered to evaluate changes to procedures, practices or equipment configuration (See Section 11—Periodic Reassessment).

Process simulations for closed systems can be performed after sterilization to confirm the acceptable
sterilization of the systems as well as the appropriateness of the procedures employed within. The duration of campaigns for closed system may be established through physical monitoring of such aspects as pressure differentials, leak rates, filter integrity tests, etc. and is further supported by a preventive maintenance program. End of campaign process simulations are thus not required for the closed portions of a process system. The duration of campaigns for open systems may be confirmed through appropriate process simulations conducted at the end of a real or simulated campaign.

2.2. Worst Case

One of the more prevalent techniques used in the validation of pharmaceutical processes is the employment of “worst case” scenarios. The use of “worst case” situations is intended to provide a greater challenge to the process, system or equipment being validated than that experienced under routine processing 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 normal situations. Process simulation tests readily lend themselves to “worst case” challenges. Some of the types of challenges which may be employed where possible are:

- using materials, equipment, utensils and other items which have remained in the aseptic processing area for extended periods after sterilization
- using the maximum number of personnel necessary to process the batch
- increasing the time period between the completion of equipment sterilization and the start of the process simulation
- using a growth promoting medium or placebo material in the process simulation test rather than an inhibitory material
- performing a process simulation test after completion of the last lot in a production campaign

The conduct of a process simulation for a sterile bulk typically includes activities and manipulations that are specific for its execution. These added steps introduce a higher potential for contamination than is inherent in the routine process and pose an increased risk for process simulation failure.

In the development of protocols or procedures used for the definition of process simulation tests, the use of “worst case” challenges such as those described above is an essential element of a well-founded program. The “worst case” challenges selected may vary based upon the specific type of process simulation utilized (see Sections 3 and 4). Risk assessment approaches such as hazard analysis and critical control point (HACCP), failure effects mode analysis (FEMA) or fault tree analysis (FTA) may be used to determine appropriate challenges.

3. PROCESS SIMULATION TEST METHODS

The application of these general procedures to any specific aseptic procedure may require modification of the methods described herein. These adaptations should be accomplished in a manner which will not improve the results of the simulation, relative to routine operations.

The conduct of process simulation tests for sterile bulk pharmaceuticals entails simulation of the process from the point of sterilization through to the completion of bulk packaging. Sterile bulk processes generally consist of a series of unit operations which in total comprise the production processes. For the purposes of process simulation it may be appropriate to conduct evaluations around either a single operation or a group of operations. Provided that all of the unit operations utilized in the production of a sterile BPC have been evaluated in an appropriate manner, the segmented approach to simulation can be as suitable as a comprehensive test involving all of the unit operations in a single simulation. The decision whether to perform the process simulation as a single integrated test or in trials based upon one or more unit operations must consider the pros and cons of each approach. It should be recognized that the decision to conduct an overall simulation or step-wise simulation approach is independent of the use of microbiological growth media or other materials in the simulation.

3.1. Total Process Simulation

In this type of simulation, the entire aseptic process is evaluated in a trial which follows the process from where the materials are first made sterile, through subdivision into containers for shipment.
Advantages

• The simulation may be able to follow the process more closely than a series of smaller simulations.

• Requires less time to complete than a series of smaller simulations.

Disadvantages

• If contamination is detected the identification and correction of sources is more difficult than in a unit operation simulation.

• In the event of failure, the entire simulation must be repeated after corrective measures have been taken.

• Will generally require the use of a single test material (either liquid or solid) throughout the entire simulation which may introduce significant differences in the simulation and how contamination might occur when compared to the routine production process.

3.2. Unit Operation(s) Simulations

In this form of simulation, a series of individual trials are conducted covering all of the steps in the aseptic process. Where the simulation is performed in several steps, the establishment of an acceptance criterion must address the cumulative contribution from each of the unit operations. Thus, the total numbers of organisms detected over the entire process must be considered.

Advantages

• If contamination is detected, the corrective measures can focus on a smaller portion of the overall process.

• Evaluation of the effects of changes to a specific part of the process can be restricted to a limited number of steps.

• In the event of failure of a portion of an individual simulation, only that simulation which failed may need to be repeated after corrective action has been taken.

• In some aseptic processes, this approach may resemble the actual process more closely.

• Allows for the use of either liquid or solid test materials in different parts of the overall simulation, which may more closely resemble actual production.

Disadvantages

• Requires more time to perform than a total process simulation.

• May require some degree of overlap to evaluate the overall process.

• The methods required to evaluate individual unit operations may require more handling of sterile materials to accommodate a segmented process simulation.

• A larger number of environmental monitoring samples must be taken during each of the individual process simulations.

4. TEST MATERIALS USED IN PROCESS SIMULATION

Independent of the decision on whether the aseptic process is to be simulated in total or in unit operation fashion, consideration must be given to the selection of a material to be utilized in the simulation. The choices are a microbiological growth promoting media, placebo material, simulation without material or actual product material (generally an excipient). With each choice there are of course certain advantages and disadvantages. Materials that inhibit microbiological growth should not be used. If a test material is utilized, a further decision between a liquid or powder material is also required. Those firms that have chosen to segment the process simulation according to the various unit operations may elect to make different selections for the test material in different parts of their overall program. For example, in sterile BPC simulations with a crystallization step, a liquid material may be used during simulation of the early steps, and a powder material in those steps which follow the crystallization step.

Inherent in the selection of a test material, and the decision to use a test material at all are considerations of potential adverse affects implicit in the use of a material. As a general rule, nothing should be introduced into the system, whether media or placebo, which may present a problem in subsequent process-
ing. The material (if used) must be able to be easily removed from the equipment in order to prevent an increased potential for contamination of production materials that would later enter the system.

See Appendix I for information on the selection, sterilization and use of test materials.

4.1. Growth Medium Simulations

A microbial growth medium in either liquid or solid state is processed in lieu of the production materials. The microbiological growth media may be tested for microbial count or sterility depending upon the acceptance criteria requirements in the protocol.

Advantages

• Allows for the direct evaluation of the aseptic processing procedures.

• Less reliance on environmental conditions in the evaluation of the process.

Disadvantages

• The microbiological growth media may be overly sensitive to antibiotic materials and other innate inhibitory materials. The use of deactivating enzymes may be necessary, however their utility in large systems may be severely limited.

• Cleaning of the process equipment after exposure to the microbiological growth media may represent a new cleaning procedure which must be developed and validated.

• It adds increased risk of microbiological contamination of the facility by providing a major nutrient source when normal materials used may be innocuous or bactericidal.

• Detection of contamination in large containers may be difficult.

• Quantities of microbiological growth media required may be excessive.

• Process simulation may have little resemblance to the actual process because of concerns regarding the media’s growth promotion capability under routine operating conditions within the equipment.

4.2. Placebo Material Simulation

A placebo material is substituted for the production materials and handled in a representative manner. The placebo material can be sampled for microbial count or sterility testing depending upon the acceptance criteria requirements of the protocol.

Advantages

• Can use materials which are able to tolerate the actual processing conditions utilized in the aseptic process.

• Placebo materials can be chosen such that their removal from the processing equipment after the simulation can be readily accomplished.

• Placebo materials can be substantially less expensive than product or microbiological growth media, which can be a significant concern in large process equipment.

Disadvantages

• Sterility or microbial count testing must be performed in order to assess whether any microorganisms are present.

• Cleaning of the process equipment after exposure to the placebo may represent a new cleaning procedure which must be developed and validated.

• The placebo material must be evaluated for lack of inhibitory effects on microorganisms.

• The sterilization of powder placebos must be validated.

• Testing of large quantities of material may be required.

4.3. Simulation Without Material

This is a simulation performed in the absence of materials. This approach has been used to evaluate process gases should be replaced with air to enhance microbial recovery.
operating procedures and personnel performing discrete aseptic manipulations, e.g., subdivision into final containers. The aseptic production processes are simulated using the procedures, personnel, equipment and components ordinarily utilized in the aseptic process. Immediately after completion of the simulation, extensive microbial sampling of product contact surfaces and personnel is performed. Alternatively or in addition, a flush of the process train with a suitable medium can be employed. The surface sampling results are utilized to determine microbial count or sterility depending upon the acceptance criteria requirements of the protocol.

Advantage

• The absence of materials eliminates cleaning (except for sampling residues, if any), microbial count or sterility testing, inhibition and recovery studies associated with the use of either a growth media or a placebo material.

Disadvantages

• The ability to detect microorganisms may be limited due to uncertainty in sampling methods and recovery efficiency.

• Conducting accurate and successful recovery validation may be difficult.

• Relies on the microbial evaluation of product contact surfaces.

4.4. Production Material Simulation

This is a simulation that is performed using actual production materials (generally an excipient). The material can be sampled for microbial count or sterility testing depending upon the acceptance criteria requirements of the protocol.

Advantages

• The process being simulated may utilize identical processing conditions as those used in production.

• The materials used for the simulation are known to be compatible with the processing equipment.

• No specialized cleaning of the equipment is necessary, the routine methods used after the production can be employed with confidence.

Disadvantages

• Sterility testing or microbial count determination must be performed.

• The production material must be evaluated for lack of inhibitory effects on microorganisms, or a neutralizing agent must be added.

• The production materials may be extremely costly.

• Testing of large quantities of material may be required.

5. EVALUATION OF SIMULATION TEST MATERIALS

Regardless of the material chosen for use in the simulation trial, it is important to evaluate that material to determine whether microorganisms were present as well as its microbial growth support characteristics.

5.1. Evaluation of Entire Test Material

The entire quantity of material (product, placebo or growth medium) utilized in the simulation is evaluated. This can be accomplished by filtration (after reconstitution for solid materials) through an appropriate sterilizing grade filter or by direct incubation of filled containers. The filter is tested to quantify the microbial bioburden of the material. Care must be taken to test (and reconstitute if necessary) using methods, controls, procedures, equipment and facilities which will not introduce contamination into the material being tested. The entire quantity of material can be subjected to microbial count or sterility testing depending upon the acceptance criteria requirements of the protocol.

Advantages

• Evaluates all of the material processed in the equipment.

Disadvantages

• Testing of large quantities of material is required which can prove quite cumbersome.

• Validation of sampling and testing methods, including the sterilization of all apparatus.
• Limited information is available for use in detecting the source of contamination in the event of failure.

• Isolation and identification of microorganisms from the filter may be difficult with certain materials.

• The test (and reconstitution) procedures may introduce contamination into the sample.

• Poorly suited to powder materials where the handling required to prepare the material for test in this fashion has substantial potential for the introduction of contamination.

• Direct incubation mandates a pass/fail acceptance criteria.

5.2. Evaluation of Test Material Samples

Samples may be taken to assess the potential for contamination at intervals during the process simulation. These samples may be of benefit in identifying when and where contamination was introduced into the process train. The use of a sampling method for either the qualitative or quantitative confirmation of process asepsis is inappropriate.

6. DOCUMENTATION

Documentation is one of the most important elements of a process simulation test program. Regulatory bodies will rely heavily on the documentation to judge the adequacy of the simulation.

The first step is to define the process to be simulated. The process generally is defined as all steps from the sterilization of the sterile BPC, solvents, reactants, containers and to the point the final sterile BPC is sealed in its shipping container. The process definition should include a description of all points that require aseptic intervention. Once the process has been clearly defined, the simulation protocol(s) or procedures can be written. These documents should include but not be limited to the following information:

• Identification of the process to be simulated

• Identification of the process train and equipment to be used

• Type of container/closure to be used

• Number of personnel participating

• Test material to be used

• Environmental monitoring to be performed

• A copy of the batch record to be used

• Acceptance criteria to be utilized

• Description of the documentation required for the final report

• Rationale for the "worst case" parameters chosen.

The above list should not be considered all-inclusive. Other factors may have to be considered due to the nature of the process to be simulated.

Execution of the protocol is generally performed through the use of a batch record. The batch record gives detailed instructions on how to perform the process simulation test(s). It should be written in the same format as a normal batch record and contain the normal data and sign-off elements. Information which normally would be attached to a batch record also should be attached to the simulation batch record, i.e., sterilization records for equipment, containers, and utensils, etc. The next step is to document the following:

• Number of organisms detected, if any

• Results of environmental testing performed.

The final report is a summation of the data from the batch record, bioburden testing of simulation material and environmental monitoring samples. Based upon this information, a conclusion is formulated regarding the acceptability of the manufacturing process and facility.

7. ENVIRONMENTAL MONITORING

Details concerning elements of an effective environmental monitoring program, including sample site selection, sample frequency, alert and action levels, methodology and interpretation of data, can be found in the literature (12).
8. ELEMENTS OF PROCESS SIMULATION TESTS

This section contains important general information to consider when conducting process simulation tests. These issues play an important role in effectively simulating the production process.

8.1. Interventions

Process simulation tests must include the normal activities that occur during an aseptic process (i.e., equipment adjustments, container-closure re-supply, sampling, etc.) in order to substantiate the acceptability of those practices in routine operation. Non-routine (corrective) interventions may be incorporated into the process simulation. It is possible that non-planned interventions may occur during the simulation and that it will be necessary to correct for fluid leakage, equipment malfunction, etc. To the extent that these types of problems occur on their own, and are rectified during a successful process simulation test, they can be defended as acceptable during normal operations (1, 13).

8.2. Duration of Simulation

Process simulation tests should be of sufficient duration to evaluate the normal manipulations necessary for the process. Activities such as initial set-up activities, changing equipment and manual maintenance operations should be included in the process simulation tests. Process simulation tests also should be of sufficient duration to include a representative number of routine and atypical interventions which might occur during an actual production operation. Where they are part of normal operations, gown changes, breaks and shift changes should be simulated. The time duration of the process simulation has greatest relevance in operations such as milling and subdivision where repetitive tasks are performed and personnel borne contamination may be of greater relevance.

8.3. Production Batch Size/Process Simulation Test Size

A process simulation test should utilize sufficient material to expose most, if not all contact surfaces to the material. It is essential that the aseptic manipulations in the simulation closely resemble those utilized in production; however the actual number need not be identical.

8.4. Incubation Conditions

It is widely accepted that process simulation tests should be incubated for a minimum of 14 days. The temperature at which the medium is incubated, however, varies from firm to firm. The temperature chosen should be based upon its ability to recover microorganisms normally found environmentally or in the product bioburden. This same panel of microorganisms should be used in growth testing the medium-filled containers. A single incubation temperature in the range of 20–35°C may be used. Data should be available to show the suitability of the selected incubation temperature to support the growth of environmental and pre-sterilization bioburden isolates. The selected temperature should be controlled and monitored continuously throughout the incubation period.

8.5. Operating Procedures

The instructions provided to the operators whether in the batch record proper or in supportive procedures must be sufficiently detailed to insure the reproducibility of the process. Process simulation instructions should follow the production procedures closely and must be similarly detailed. Close correspondence between the production and process simulation methodology confirms the acceptability of the procedures utilized.

When the production batch size is small, there may be greater prevalence of manual operations in the preparation of sterile products. The process simulation of a manual process of this sort is carried out in accordance with the methods and practices outlined in this document, with one addition. Each operator who performs this type of manual process should be individually evaluated to establish the acceptability of their aseptic technique.

8.6. Staffing Considerations

Each person who works in an aseptic production suite should participate in a successful process simulation test on a periodic basis.

8.7. Campaigns

Multiple lots of sterile BPCs may be produced following a single sterilization without intervening cleaning of the equipment requiring a breech in the integrity of the system. The process simulation program should
confirm the acceptability of this production mode for open systems. The simulation should be planned to effectively balance the goals of simulating, as closely as possible, the actual manufacturing process, and minimizing those conditions that would inhibit the recovery of microorganisms. As stated previously the duration of campaign length for closed systems is established through preventive maintenance and monitoring of physical data from the system.

8.8. Equipment Qualification

Process equipment and utility systems used in the preparation of sterile bulk systems should be subjected to documented qualification to confirm their acceptability for their intended use. This should include installation considerations including drawings, materials of construction, calibration, preventive maintenance program, etc.

Of equal importance is the operational phase of the qualification in which operating procedures are verified, along with leak rates and pressure differentials. A part of this confirmation is measurement of process and equipment variables during the simulated execution of the process. This confirmation can be used to establish a baseline of acceptable performance for the equipment which can be used to support the continued integrity of the process train over the length of a production campaign.

9. INTERPRETATION OF RESULTS AND ACCEPTANCE CRITERIA

9.1. Background

The adoption of limits and acceptance criteria for process simulation tests is one of the more contentious subjects within the industry in recent years. Whatever the number of organisms allowed in a process simulation, the ultimate goal for the number of organisms in any process simulation test (at either the bulk or filling stage) should be zero (4).

The acceptance criteria utilized for the simulation can be either qualitative (pass/fail) or quantitative (CFU/simulation). The criterion choice depends upon the simulation methods utilized.

The selection of acceptance criteria for aseptic processing validation is the central issue to be resolved in the conduct of process simulation tests. This section offers guidance which can be used to establish appropriate limits and acceptance criteria for aseptic process simulation tests.

9.2. Approaches for Acceptance Criteria

9.2.1. Quantitative

The dominant methodology for the validation of aseptic processes utilized for drug product compounding and filling utilizes a media process simulation approach. In conjunction with the execution of this evaluation, a firm typically selects an acceptance criterion (8). An adaptation of the final product container approach, that relies on a quantitative assessment of contamination levels, for sterile bulks is possible.

A microbiological growth medium is designed specifically to support or stimulate the growth of microorganisms. As it is a more rigorous challenge than processed products, which often provide neutral and sometimes hostile microbial growth environments, some low number other than zero is chosen as an acceptance criterion. Nevertheless, a contaminated process simulation should be a rare occurrence. Any contamination in a process simulation must be investigated.

There are, however, significant technical problems in achieving this goal. Microbiological growth media and simulated products do not match real products perfectly in terms of their processing characteristics and microbiological growth support properties. Direct application of the process simulation acceptance criteria for aseptic filling to sterile bulk pharmaceutical chemicals is inappropriate for a number of reasons including:

- introduction of extra processing equipment;
- added aseptic manipulations;
- relatively few large containers are required;
- inspectional difficulties in large containers;
- the amount of microbiological growth media required;
- and cleaning growth media from process equipment.
Microbiological growth media differ in many respects from the products they are intended to simulate; for example, there are differences in solubility, pH, filtration rates and filterability and viscosity. With powders, the process simulation test involves reconstituting powdered media or simulated product, with the inherent added risk of contamination.

Process simulation testing for sterile bulk materials is conducted using either a placebo material, product material or a growth medium (either solid or fluid) which contacts equipment surfaces in like manner to the product being simulated. After completion of the simulation test, the material is evaluated. The number of colony forming units detected in the material can be used to project a worst case contamination rate based on the smallest bulk production batch and the largest finished product container of the product being simulated (i.e., the fewest number of finished product units filled from the entire batch).

The sterile bulk process simulation test passes if the contamination rate projects to not more than 1 positive unit in 10,000 finished dosage units (or NMT 0.0001 CFU/unit). This is derived from FDA's latest Guidance on Sterile Drug Products Produced by Aseptic Processing (14).

The simulation batch size may differ from the production batch size provided the aseptic manipulations are essentially the same, and adequate mixing and agitation of the simulation batch can be achieved in the process equipment.

When material from more than one process train is combined to produce the finished sterile bulk and it is not possible to simulate the entire process, the projected contamination rate for the finished bulk is the sum of the process simulation test results from each individually evaluated process train.

Consider the following examples:

**Example 1**

Minimum production batch size 200 kg, maximum finished drug product fill 10 g, chosen placebo size 60 kg, 2 CFU detected in the simulation.

1. The contamination level for the simulation batch is 2 CFU. It projects to 2 CFU in the production batch.

2. Determine the minimum number of dosage forms produced from the production batch.

\[
200,000 \text{ g/batch} / 10 \text{ g/unit} = 20,000 \text{ units/batch}
\]

3. Calculate the maximum CFU/unit and compare to the limit of NMT 0.0001 CFU/unit.

\[
2 \text{ CFU/batch} / 20,000 \text{ units/batch} = 0.0001 \text{ CFU/unit}
\]

Since the projected contamination rate 0.0001 CFU/unit does not exceed the limit of NMT 0.0001 CFU/unit the process simulation test passes.

**Example 2**

Minimum production batch size 200 kg, maximum finished drug product fill 5 g, chosen placebo size 60 kg, 5 CFU detected in the simulation.

1. The contamination level for the simulation batch is 5 CFU. It projects to 5 CFU in the production batch.

2. Determine the minimum number of dosage forms produced from the production batch.

\[
200,000 \text{ g/batch} / 5 \text{ g/unit} = 40,000 \text{ units/batch}
\]

3. Calculate the maximum CFU/unit and compare to the limit of NMT 0.0001 CFU/unit.

\[
5 \text{ CFU/batch} / 40,000 \text{ units/batch} = 0.000125 \text{ CFU/unit}
\]

Since the projected contamination rate 0.000125 CFU/unit exceeds the limit of NMT 0.0001 CFU/unit the process simulation test fails.

**Example 3**

Minimum production batch size 200 kg, maximum finished drug product fill 1 g, chosen placebo size 60 kg. The finished bulk is produced from material from process trains A and B, respectively, blended together in process train C. 2 CFU detected in the process train A placebo, 3 CFU detected in the process train B placebo, and 2 CFU detected in the process train C placebo after simulation.

1. The combined contamination level for the simulation batches is 7 CFU. It projects to 7 CFU in the production batch.
2. **Determine the minimum number of dosage forms produced from the production batch.**

\[
200,000 \text{ g/batch/1 g/unit} = 200,000 \text{ units/batch}
\]

3. **Calculate the maximum CFU/unit and compare to the limit of NMT 0.0001 CFU/unit.**

\[
7 \text{ CFU/batch/200,000 units/batch} = 0.000035 \text{ CFU/unit}
\]

Since the projected contamination rate 0.000035 CFU/unit does not exceed the limit of NMT 0.0001 CFU/unit the cumulative process simulation test passes.

**NOTE:** Microbial count determination has similarities to the sterility test and contamination may be introduced as a consequence of the test environment, personnel and procedures employed. Validation of the test method for the material is essential to the success of this approach.

The use of a non-zero contamination rate mimics the approach used for dosage forms. The suggested approach requires tight (albeit, not absolute) control over the extent of microbial contamination acceptable in a process simulation and allows for further improvement as technology and procedures are improved. Most importantly it enables meaningful evaluation of aseptic processing procedures for sterile bulks using a quantitative approach.

**9.2.2. Qualitative**

Any process simulation can be evaluated using a qualitative (pass/fail) criterion. A qualitative approach can be used with any of the simulation methods. While it can offer handling advantages (relative to quantitative testing), it precludes recognition of the aseptic process simulation sampling and testing manipulations as a possible contributor to the presence of organisms since zero growth is the only acceptable option.

**10. FAILURE INVESTIGATION AND CORRECTIVE ACTION**

A comprehensive sampling and microbial identification scheme is crucial in the investigation and determination of source of any detected microbial contamination. In the instance when the process simulation test exhibits contamination possible sources of that contamination must be investigated. A detailed history of the investigation needs to be maintained.

Based upon the outcome of the investigation, the cause of the failure is either assignable or not assignable. It may be clearly assignable to a single source, or vaguely associated with multiple systems or processes which require redefining. If the cause is assignable, corrective action needs to be taken and documented. The root cause and the corrective action will dictate the number of process simulation tests required to demonstrate that the process is operating within the expected parameters. If no cause can be found, the process should be validated as though it were a new process. Multiple consecutive process simulation tests should be performed to demonstrate the ability to consistently produce acceptable product.

**11. PERIODIC REASSESSMENT**

Each firm should determine the frequency of and interval between periodic simulation of each process. An annual evaluation of the need to perform a process simulation should be sufficient.

Unscheduled process simulation tests may be required following a significant change. In such cases, the number of process simulation tests may vary, depending upon the extent of the change. Examples of such changes include:

- Major modifications to the equipment (interchanging standard parts does not constitute a major equipment modification)
- Modification to equipment or facilities that potentially affects the air quality or airflow in the aseptic environment
- Increases beyond the maximum number of production personnel used in process simulation testing
- Major changes to the aseptic production process and/or procedures.
- Introduction of a new fill volume larger than prior fills.

It also may be necessary to perform process simulation tests in response to adverse trends or failures in the on-going monitoring of the facility, equipment, personnel, environment or process.
APPENDIX 1. SELECTION AND STERILIZATION OF TEST MATERIALS

In the conduct of aseptic process simulation tests for sterile BPC, the use of a sterile placebo material may be appropriate. Care must be taken in the choice of material to be used, and in its preparation, to avoid difficulties with the process simulation testing program. Depending upon the specific process equipment, and operating procedures, it may be appropriate to utilize a liquid or a powder as a test material. Consideration can also be given to the use of a growth promoting material or an inert material. In certain situations more than one test material can be utilized for different parts of the simulation program. Whenever material is utilized in the simulation, it should be processed and ultimately packaged as closely as possible to the sterile BPC being simulated.

**Selection of Test Powder:** The selection of powder test material for use in process simulation testing must consider several factors. The seemingly obvious choice of dry sterile microbiological growth media, itself, has proven less than successful because of its poor flow properties, which make its passage through sterile powder process equipment a considerable challenge. The principal placebo materials which have been used successfully are lactose, mannitol, and polyethylene glycol. The most common choice for a powder media is dry Soybean-Casein Digest Medium (SCDM), though other choices are certainly possible. The chosen material must be easily sterilizable, dispersible or dissolvable in the chosen medium with minimal agitation, have no adverse effect on growth promotion, and be easily handled in the simulation process equipment.

**Selection of Test Liquid:** The selection of a liquid test material is governed by several considerations. The use of a microbiological growth media is certainly possible; the most common objection to their use relate to concerns with the cleaning of residual media after completion of the simulation. Liquid media which have been utilized for process simulation include SCDM and peptone broth. Dilution of the media to lower strengths is employed and is acceptable provided growth promotion can be demonstrated (see below). Potential placebo fluids may range from Water for Injection to one of the solvents employed in the process, assuming the solvent has no significant antimicrobial activity. Test liquids are generally sterilized by 0.2 micron filtration using the housings required for the process.

**Sterilization of Test Powder (placebo or growth media):** Part of the selection process requires the identification of a suitable sterilization method for the chosen material. The material being evaluated should be subjected to a validated sterilization process prior to the process simulation tests. The validation study should include verification that the sterilization process has no significant adverse effect on the material’s properties. The most common sterilization method in use is irradiation in the same final container as used for the sterile powder being simulated. Alternatively, the material can be sterilized by dry heat or filtration, followed by bulk lyophilization. Along with the placebo material prepared for use in the filling trial, additional material in separate bags can be utilized for sterility testing after sterilization. The test samples can be tested if there is any question regarding the sterility of the material.

**Inhibition Testing for Placebo Materials:** Growth promotion testing, in which the chosen material is tested for potential inhibition, is performed using *Bacillus subtilis* (ATCC 6633) and *Candida albicans* (ATCC 10231). Consideration should be given to testing with other microorganisms commonly found in the aseptic processing area environment, such as those isolated during facility, equipment, personnel monitoring and sterility testing. Replicate samples of the placebo materials are inoculated with 10-100 CFU of each of the challenge organisms and then dissolved/dispersed in sterile medium. Positive controls are prepared by inoculating replicate tubes of medium which do not contain the sterilized placebo material. Growth must be evident in all tubes within seven days after incubation at 20-25°C. Growth promotion for liquid placebos is performed in a similar fashion after inoculation, using either direct plating or membrane filtration of the liquid placebo. The filters are then tested as if for a membrane sterility test and growth must appear within 7 days of incubation at 20–25°C.

**Growth Promotion for Growth Media:** Confirmation of the media’s growth promotion properties is an essential element. The conduct of media growth promotion evaluation is a relatively simple procedure, with a few basic requirements. The media utilized for the growth promotion studies should be drawn from the same material utilized for the process simulation itself. The growth promotion units should be inocu-
lated with a low concentration (less than 100 organisms per container) of the USP growth promotion organisms—*Bacillus subtilis* & *Candida albicans*. Consideration should be given to testing additional units with other organisms commonly found in the aseptic processing area environment, such as the organisms isolated during facility, equipment, personnel monitoring, sterility testing, etc.

Media growth promotion studies can be performed prior to, concurrent with or after the completion of the process simulation incubation period. When growth promotion is performed before incubation, the acceptability of the media is confirmed prior to the simulation. Pre-simulation testing cannot confirm the acceptability of the media used in the actual trial and either concurrent or post-incubation growth promotion must be employed as well. The use of concurrent testing appears preferable as the results will then be available prior to completion of the incubation. Post-incubation growth promotion provides a similar degree of assurance, but the delay in obtaining results effectively extends the length of time before the process simulation results are definitive.

**APPENDIX 2, DEFINITIONS**

**aseptic (asepsis)**

Free from disease-producing microorganisms.

**aseptic filling**

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, 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, materials, equipment and personnel are regulated to control microbial and particulate contamination to acceptable levels.

**closed system (see system, closed)**

**colony forming unit (CFU)**

Visible outcome of growth of microorganisms arising from a single or multiple cells.

**environmental monitoring program**

Defined documented program which describes the routine particulate and microbiological monitoring of processing and manufacturing areas, and includes a corrective action plan when action levels are exceeded. It includes assessment of environmental air, surfaces and personnel.

**growth promotion test**

Test performed to demonstrate that media will support microbial growth.

**microbial count determination**

A test performed to quantify the number of microorganisms present in a sample of material. Standard microbial methods are utilized to estimate the number of colony forming units (CFU) per unit mass or volume.

**open system (see system, open)**

**process simulation (without microbiological growth media)**

Method of evaluating an aseptic process employing methods which closely approximate those used for sterile materials using an appropriate material.

**process simulation (with microbiological growth media)**

Method of evaluating an aseptic process using a microbial growth medium employing methods which closely approximate those used for sterile materials.

**sterile**

Free of any viable organisms.
NOTE: In practice, no such absolute statement regarding the absence of microorganisms can be proven (see sterilization).

**sterility assurance level (SAL)**

Probability that a batch of product is sterile.

**sterile bulk pharmaceutical chemical**

A sterile material derived from chemical, fermentation or semi-synthetic sources which is final packaged or stored in bulk form. The bulk material may be an active pharmaceutical, or excipient. Sterile BPCs can be solids, solutions or suspensions.

**sterility test**

Test performed to determine if viable microorganisms are present.

**sterilization**

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

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.

**system, closed**

A "closed" system is sterilized-in-place or sterilized while closed prior to use using a validated procedure, is pressure and/or vacuum tight to some predefined leak rate maintained through the length of the campaign, can be utilized for its intended purpose without breach to the integrity of the system, can be adapted for fluid transfers in and/or out while maintaining asepsis, is connectable to other closed systems while maintaining integrity of all closed systems (e.g., Rapid Transfer Port, steamed connection, etc.), is safeguarded from any loss of integrity by scheduled preventive maintenance and utilizes sterilizing filters for sterilization of process streams which are integrity tested and traceable to each product lot.

**system, open**

A system which fails to meet one or more of the criteria which define a closed system.

**unit operation**

A processing activity involving multiple steps which affects a single type of change to the materials (e.g., reaction, crystallization, filtration, drying, milling, etc.) usually carried out in a single piece of equipment. Individual unit operations can be performed in either "open" or "closed" systems as dictated by the equipment design.

**worst case**

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

**APPENDIX 3, REFERENCES**


