Technicial Report No. 22

Process Simulation Testing for Aseptically Filled Products

PDA Journal of Pharmaceutical Science and Technology

1996

Supplement

Volume 50

Number S1

PDA

An International Association For Pharmaceutical Science And Technology

PDA
PROCESS SIMULATION TESTING FOR ASEPTICALLY FILLED PRODUCTS

PDA
ASEPTIC PROCESSING MONOGRAPH REVISION TASK FORCE

September 1996

James P. Agalloco. Agalloco & Associates (Co-chair)
James E. Akers, Ph.D., Akers Kennedy & Associates, Inc.
Doris L. Conrad, SmithKline Beecham (Co-chair)
William R. Frieben, Ph.D., Pharmacia & Upjohn, Inc.
Edmund M. Fry, PDA
Carol M. Lampe, Baxter Healthcare Corporation
Russell E. Madsen, PDA
William R. McCullers, Merck & Company, Inc.
Terry E. Munson, Kemper-Masterson, Inc.
Ronald F. Tetzlaff, Ph.D., Kemper-Masterson, Inc.
James D. Wilson, Isomedix, Inc.

Process Simulation Testing for Aseptically Filled Products

Technical Report No. 22

PDA

PDA
PROCESS SIMULATION TESTING FOR ASEPTICALLY FILLED PRODUCTS

PDA
ASEPTIC PROCESSING MONOGRAPH REVISION TASK FORCE

September 1996

James P. Agalloco. Agalloco & Associates (Co-chair)
James E. Akers, Ph.D., Akers Kennedy & Associates, Inc.
Doris L. Conrad, SmithKline Beecham (Co-chair)
William R. Frieben, Ph.D., Pharmacia & Upjohn, Inc.
Edmund M. Fry, PDA
Carol M. Lampe, Baxter Healthcare Corporation
Russell E. Madsen, PDA
William R. McCullers, Merck & Company, Inc.
Terry E. Munson, Kemper-Masterson, Inc.
Ronald F. Tetzlaff, Ph.D., Kemper-Masterson, Inc.
James D. Wilson, Isomedix, Inc.

PREFACE

This document replaces the previous PDA technical documents on the validation of aseptic processing: Technical Monograph No. 2, *Validation of Aseptic Filling for Solution Drug Products,* 1980; and Technical Report No. 6, *Validation of Aseptic Drug Powder Filling Processes,* 1984. Our intent in this effort was to update these documents and expand the coverage to other dosage forms, as well as embrace the changing nature of 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.

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 aseptic processing operations. We have also drawn heavily upon the responses received from the 1992 PDA survey on aseptic processing. The task force believes the use of survey information provides the most accurate information on industry practice.

Despite the use of an "open process" and consideration of survey information, this document should be considered as a guide; it is not intended to establish any mandatory or implied standard. This is especially true in areas such as "blow-fill-seal" and "isolation" where the rate of technological progress has been extremely rapid.

James P. Agalloco
Doris L. Conrad
Co-chairs, Aseptic Processing Monograph Revision Task Force

TABLE OF CONTENTS

1. INTRODUCTION S1
   1.1 Previous Monographs S1
   1.2 Reason for Revision S1
   1.3 Scope S1
   1.4 Purpose S1
   1.5 Considerations S1
2. PROCESS SIMULATION CONCEPTS AND PRINCIPLES S1
   2.1 Number and Frequency of Tests S1
   2.2 Worst Case S2
3. PROCESS SIMULATION TEST METHODS S2
   3.1 Solutions S2
   3.2 Lyophilized Products S3
   3.3 Suspensions S4
   3.4 Ointments/Creams/Emulsions/Gels S4
   3.5 Powders S4
   3.6 Other Dosage Forms S6
   3.7 Advanced Aseptic Processing Technologies S6
4. DOCUMENTATION S6
   4.1 Process Definition S6
   4.2 Protocol Preparation S6
   4.3 Protocol Execution S7
5. MICROBIOLOGICAL ENVIRONMENTAL MONITORING S7
6. ELEMENTS OF PROCESS SIMULATION TESTS S7
   6.1 Set-Up S7
   6.2 Interventions S7
   6.3 Container Size S7
   6.4 Container/Closure Configuration S7
   6.5 Filling Speed S8
   6.6 Fill Volume S8
   6.7 Duration of Fill S8
   6.8 Production Batch Size/Process Simulation Test Size S8
   6.9 Manual Filing S8
   6.10 Incubation Conditions S9
   6.11 Media Selection S9
   6.12 Media Growth Promotion S9
   6.13 Container Inspection S9
   6.14 Inert Gassing S9
   6.15 Facility Considerations S10
   6.16 Staffing Considerations S10
7. INTERPRETATION OF RESULTS AND ACCEPTANCE CRITERIA S10
   7.1 Background S10
   7.2 Strategies S10
   7.3 Guidance S10
8. FAILURE INVESTIGATION AND CORRECTIVE ACTION S11
9. VALIDATION MAINTENANCE S12

APPENDIX 1: SELECTION AND STERILIZATION OF PLACEBO POWDER MATERIALS S13

APPENDIX 2: DEFINITIONS S14

APPENDIX 3: REFERENCES S16

Process Simulation Testing for Aseptically Filled Products

1. INTRODUCTION

1.1 Previous Monographs

PDA has published two guides which focused on the aseptic filling process: Technical Monograph No. 2, *Validation of Aseptic Filling for Solution Drug Products,* 1980, and Technical Report No. 6, *Validation of Aseptic Drug Powder Filling Processes,* 1984.

1.2 Reason for Revision

Since those reports were issued, there have been significant advances in facility and equipment design, such as the use of barrier, isolation and blow-fill-seal technology. These developments warrant publication of a current single guidance document on issues relating to the control of sterile dosage form aseptic processing.

1.3 Scope

This document addresses the validation of aseptic processing during pharmaceutical and biopharmaceutical formulation and filling activities (referred to as secondary manufacturing in many parts of the world). It describes methods and procedures for the conduct of process simulation tests, including formulation and filling of aseptically processed pharmaceutical dosage forms. Aseptic operations required in the preparation of sterile bulk materials and biotechnology procedures are not a part of this document. While the focus of this document is on aseptic processing in the pharmaceutical and biopharmaceutical industry, application of the concepts to the preparation of sterile medical devices and diagnostics may be appropriate.

1.4 Purpose

One of the most useful methods for evaluating the capabilities of an aseptic processing operation is the process simulation test (media fill). It is a simulation of the entire aseptic formulation and filling process, which substitutes a microbiological growth medium for a sterile product.

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.

The purpose of a process simulation test is to:

- Demonstrate the capability of the aseptic process to produce sterile drug products
- Qualify or certify aseptic processing personnel
- Comply with current Good Manufacturing Practice requirements

1.5 Considerations

Despite the widespread use of process simulation testing as a component of a validation program for aseptic processing operations, not all in the pharmaceutical industry agree that the test is an essential part of a validation program for such operations. Proponents of the process simulation test argue that this method allows a quantitative estimate of the contamination rates during aseptic processing. Opponents, on the other hand, cite the many problems and difficulties in using the method, such as the large number of containers required to be filled, failure of the method to simulate operating conditions and concern over using a microbiological growth medium in the aseptic processing area.

Although legitimate concerns and problems exist in using the process simulation test, it can provide an excellent method for evaluating an aseptic processing operation, so long as its limitations are recognized and taken into account in interpreting the results. For example, the process simulation test does not provide information which relates directly to the sterility of a specific product batch. Therefore, the fact that a specific process simulation test does not meet the required acceptance criteria does not necessarily indicate a sterility problem for any particular production batch. However, it does provide a tool for evaluating the processing steps used to manufacture a sterile product.

A holistic approach must be used to validate adequately 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 drug products produced on the same line at other times will have the same level of microbiological quality. However, through control and validation of all 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 all of the related sanitization and sterilization processes independently, such as sterilization/depyrogenation of the product, container, closure and all product contact surfaces.

2. PROCESS SIMULATION CONCEPTS AND PRINCIPLES

2.1 Number and Frequency of Tests

For a new facility or production process, process simulations are performed as part of the overall validation. Initial process simulation tests generally are conducted after equipment qualification and 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. If a process simulation test fails in the absence of this supportive work, identification of a possible cause

will be more difficult. Generally, three consecutive successful process simulation tests are performed when qualifying a new facility or filling line, or validating a process. Prior to release of the new facility, filling line or process for production use, acceptable results from these consecutive tests should be achieved to demonstrate the reproducibility of the process.

In existing facilities, there should be a routine process simulation test program for each aseptic filling line, which should be performed at least twice per year. A six-month interval between simulation trials for an aseptic filling process is widely practiced in the parenteral industry. Although this interval has evolved largely from historical experience and regulatory expectations, and apparently has no firm scientific rationale, it appears workable for many aseptic processing areas where a six-month operating period without intentional shutdown for preventive maintenance is scheduled.

Additional process simulation tests should be performed to evaluate changes to procedures, practices or equipment configuration. (See Section 9—Validation Maintenance.)

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. 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 are:

- Using materials, components and closures which have remained in the aseptic processing area for extended periods
- Increasing the size of the fill crew to more than the number necessary to fill the batch
- On a particular line, filling the smallest units at the fastest speed (handling difficulty) and the largest units at the slowest operating speed (maximizing exposure)
- Using a growth promoting medium in the process simulation test rather than an inhibitory and preserved formulation

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. Formalized 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 conduct of process simulation tests for aseptically produced parenteral products entails simulation of the process from the point of sterilization through to the completion of filling. The aseptic procedures used during dosage form compounding are a necessary part of the studies to be performed. This section summarizes considerations to be made in the performance of process simulation tests for aseptically produced solutions, lyophiles, suspensions, ointments and powders.

This document provides an outline of the methods used to validate the aseptic techniques used in the preparation of sterile pharmaceuticals. This validation effort is accomplished largely through the use of simulated production operations in which a sterile growth medium is handled in a manner which closely approximates the methods used for sterile materials. 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.

3.1 Solutions

Compounding Operations – A quantity of suitable growth medium is sterilized by filtration or steam sterilization (in bulk tanks) in a manner similar to the production process being simulated. After sterilization, the medium is passed through the equipment train as though it were an actual product batch, and all routine procedures used in the manufacture of a batch are performed, i.e., sampling, filter integrity testing etc. Once the medium has been transferred to the holding vessel from which filling proceeds, it is held for a period of time at least equal to that for aseptically produced materials. Any aseptic manipulations performed during and at the end of the holding period should be simulated as well, i.e., sampling, re-filtration, hold times and product recirculation.

Filling Operations – The containers, and closures if necessary, are cleaned and sterilized using standard operating procedures (SOPs), as are equipment and filling parts. The filling machine is operated at the pre-determined fill rate for the container size being utilized. (See Section 2.2 for guidance on "worst case" conditions.) The containers are sealed and the medium-filled units are collected in sequentially numbered trays or boxes. It may be useful to note the time of collection. The filled units should be briefly inverted and swirled after filling to assure closure contact with the medium. The process simulation test is videotaped and/or observed to gain further insight into problem resolution. All routine activities which take place on the filling line should be a part of the simulation procedure, i.e., weight adjustments, replenishment of containers, addition of components, change of filling pump, change of filter etc. An expanded discussion of these and other considerations in the conduct of process simulation tests is presented elsewhere in this document. (See Section 4–Documentation.)

3.2 Lyophilized Products

Most lyophilized products are aseptically filled solutions which are transferred to sterile lyophilization chambers after filling. Within the industry, various container-closure systems are used, e.g., vial with fluted stopper, vial with combination stopper and crimp, multi-chambered vial, pre-filled multi-chamber syringe or ampule. The less common packages may require further adaptation of the methods described in this section.

Compounding Operations—See Section 3.1 on compounding of solution products.

Filling Operations—See Section 3.1 on filling of solution products.

Lyophilization Operations—The methods employed for lyophilization process simulation testing generally are similar to those used for solution fills with the addition of the transport and freeze-drying steps. Presented below are several possible means for evaluation of these activities; other approaches are possible.

3.2.1 *Lyophilization of Dilute Medium* – Containers are filled with a diluted medium, and stoppers are partially inserted in the necks. The containers are transported to the freeze dryer and lyophilized, until the concentration in the container approximates that of a full strength medium. The stoppers then are seated within the lyophilization chamber. The stoppered units are removed from the aseptic processing area and sealed.

Advantage(s)

Simulates the entire lyophilization process.

Disadvantage(s)

Time-consuming to perform, as a complete lyophilization cycle must be performed.

Medium lyophilization process needs some development, and may not resemble the lyophilization process used for any product.

Growth promotion may vary with final concentration of medium in the lyophilized container.

The medium is frozen during the process and may not support microbial growth.

3.2.2 *Simulated Lyophilization* – Containers are filled with medium, and stoppers are partially inserted in the necks. The containers are transported and loaded into the lyophilizer. A full, or partial vacuum is drawn on the chamber at ambient temperature, and maintained for the duration of a normal lyophilization process. The chamber is then vented and the stoppers are seated within the chamber. The stoppered units are removed from the aseptic area and sealed.

Advantage(s)

The medium is not frozen. Therefore, there are fewer concerns with regard to microbial survival in a freezing process or the ability of the medium to support growth.

Disadvantage(s)

Time-consuming to perform, extending through the entire lyophilization cycle.

The vacuum must not be so low as to permit the medium in the container to boil out.

3.2.3 *Simulated Load/Unload with Shortened Hold Time.* – Containers are filled with medium, and stoppers are partially inserted. The containers are loaded into the lyophilizer. A partial vacuum is drawn on the chamber and this level is held for a pre-determined time. The chamber is then vented and the stoppers are seated within the chamber. The stoppered units are removed from the aseptic processing area and sealed.

Advantage(s)

The medium is not frozen. Therefore, there are fewer concerns with regard to microbial survival in a freezing process or the ability of the medium to support growth.

Focuses on loading and sealing activities, which are presumed to be the greatest source of potential contamination.

Disadvantage(s)

Shortened exposure time in lyophilization chamber may not simulate the lyophilization process duration adequately.

The vacuum must not be so low as to permit the medium in the container to boil out.

3.2.4 *Special Considerations Unique to the Production of Lyophilized Products*

3.2.4.1 *Freezing of Media* – Process simulation tests should simulate production operations as closely as possible, clearly implying that the medium be frozen during the trial. If this advice is followed, the ability of the medium to support the growth of low numbers of organisms introduced prior to freezing should be confirmed. This concern may be avoided by not freezing the medium in the lyophilization chamber.

3.2.4.2 *Vacuum Levels and Duration* – In the simulation of a lyophilization process, the depth of vacuum drawn on the chamber and the period of time for which this vacuum is held are important considerations. Where the medium is frozen (see Section 3.2.4.1), the level of vacuum drawn is not significant, however its duration may be problematic for organisms requiring the presence of oxygen for growth. If the medium is not frozen, the vacuum must not be so low as to permit the medium in the container to boil out, thereby invalidating the test.

3.2.4.3 *Anaerobic Conditions* – It is common in the production of lyophilized products to utilize sterile inert gasses to break the vacuum on the chamber and remain in the container after sealing. Where Soybean-Casein Digest Medium is used for the conduct of the process simulation test, consideration should be given to using air rather than an inert gas to assure aerobic conditions for the process simulation test. The use of an inert gas and anaerobic medium (e.g., Alternate Fluid Thioglycollate Medium) would be appropriate where the presence of anaerobic organisms has been confirmed in either environmental monitoring or, more likely, during end product sterility testing. Where anaerobes have not been detected in the environmental monitoring or sterility testing, lyophilizer process simulation tests should utilize Soybean-Casein Digest Medium and air.

3.3 Suspensions

Sterile suspensions are not as prevalent as solutions, however they are used for the administration of insoluble sterile materials such as antibiotics, vaccines and corticosteroids. The conduct of a process simulation test for suspension filling requires the use of procedures which mimic those used in the manufacture and filling of suspensions.

Compounding Operations – The preparation of the sterile medium is completed as described previously in Section 3.1. The simulation procedures are extended to include the particular aspects of suspension manufacturing including sterilization of the vehicle, addition of the sterile powder and homogenization of the suspension. The most basic adaptation of the standard liquid process simulation test is the addition of a sterile placebo powder to a tank of medium. This simulates the critical difference in the production of suspensions: the addition of a sterile solid under aseptic conditions. The homogenization of the medium may affect the growth promotion properties of the medium.

NOTE: See Appendix 1 for a description of the placebo material selection, sterilization and evaluation.

Filling Operations – These are carried out in a manner similar to that described for solution fills, with the introduction of any routine changes in the filling set-up to accommodate suspension filling. Where recycle lines, surge tanks, agitators and other modifications are employed to fill suspensions, they should be employed in the simulated fill. As previously stated, all routine line operations should be part of the simulation.

3.4 Ointments/Creams/Emulsions/Gels

Sterile ointment, cream, emulsion and gel production processes can resemble either solution or suspension products, depending upon the solubility of the active and inactive materials in the bases. The simulation should mimic the actual procedures used by the firm in their operations.

Compounding Operations – Follow the procedures previously described for either solution or suspension compounding, using whichever method more closely mimics the actual compounding procedure used for the product being simulated. It may be necessary to increase the viscosity of the medium to more closely resemble the product's filling characteristics.

Filling Operations – Filling of sterile ointments generally is performed on a filling machine quite different from one employed for vials, syringes or ampules. The differences in equipment design and operation aside, the basic approach to the conduct of the fill is virtually identical to that employed for other packages.

3.4.1 *Special Considerations Unique to the Production of Sterile Ointments, Creams, Emulsions and Gels*

Inspection of units – The post-incubation inspection of filled process simulation test tubes may require extra care. When opaque containers are filled, it is common to extrude the material from the individual tubes into glass containers for inspection. Care must be taken in the extrusion and inspection, to assure growth will be detected. Alternatively, special tubes which do not contain the opacifying agent may be purchased for the process simulation test.

3.5 Powders

The production of sterile powders requires processes and equipment quite different from that used for the production of other aseptically produced sterile dosage forms.

Compounding Operations – These activities should be included if sterile bulk actives are blended with sterile buffers, preservatives or solubilizing agents prior to filling. Blending, milling, subdivision and other procedures carried out at the filling site can be simulated using an appropriate placebo powder using the same methods as those employed for the process.

NOTE: See Appendix 1 for a description of the placebo material selection, sterilization and evaluation.

NOTE: The simulation of aseptic processes utilized for the manufacture and isolation of sterile bulk powders is *not* part of this document.

Filling Operations – The filling of dry powders utilizes equipment quite different from that used for filling liquids. In order to perform a process simulation test for a powder filling procedure, adaptations to the filling practices must be employed. It should be noted that utilization of medium in the evaluation of a dry powder fill process often requires two individual filling operations (one each for the liquid medium and the placebo powder). The individual contamination contribution from each of these individual filling steps may increase the overall potential for contamination. The methods outlined below may be used for the evaluation of a powder filling process through a process simulation test procedure. The fill operations may be carried out either on-line (a fill activity performed as part of a continuous process with minimal manipulation) or off-line (a fill activity performed as part of a discontinuous process with greater manipulation).

3.5.1 *Liquid medium filled by the powder filling equipment* – A limited number of sterile powder filling machines are capable of liquid filling with little or no modification. While these units may not fill liquids to the same degree of consistency with which they fill powders, their flexibility greatly simplifies the process simulation test. In this procedure, the liquid medium is introduced as a direct substitute for the sterile powder in the fill hopper. The methods used to introduce the medium, of course, are different from those utilized when powder filling, but that is a minor adaptation to the process when contrasted with the modifications necessary for other fillers. The conduct of the process simulation test is essentially the same as that described in Section 3.1,

integrating all of the routine fill line activities during the simulation.

Advantage(s)

Only a single fill machine is required; a separate liquid filler is not necessary. This greatly simplifies the conduct of the process simulation test.

Additional media controls for the liquid fill machine are not required (see below).

Disadvantage(s)

Feed set-up may differ from that used for powder fill.

3.5.2 *Specialized Filling Machine* – Some manufacturers of dry powder fillers offer adaptations to their machines which can add a supplementary liquid filling capability. The liquid filling capability of these machines is not equivalent to a conventional liquid filler, and is used only in process simulation tests. In this manner, the same filling machine could be used for both the liquid and solid filling operation.

Advantage(s)

No off-line manipulation of the components and the units filled with medium.

Single filler; no additional line modifications required.

Disadvantage(s)

May need to be operated at lower speeds due to the design of the filler.

Some designs may not fill liquid into every vial which receives powder.

3.5.3 *On-line liquid fill followed by on-line powder fill* – In this approach, a liquid filling machine is added to the filling line prior to the powder filler. A volume of medium (in the range appropriate for a liquid fill) is added to the container, followed by a fill of a sterile placebo material. The choice between this method and that in 3.5.4 is governed largely by the dictates of space on the filling line.

Advantage(s)

All processes on-line; no additional handling of containers.

Disadvantage(s)

Second filler to set up and validate.

3.5.4 *On-line powder fill followed by on-line liquid fill* – This method is used where the physical addition of a liquid filler before the powder filler is not possible.

Advantage(s)

All processes on-line, no additional handling of containers.

Disadvantage(s)

Second filler to set up and validate.

Potential for powder aspiration from the container when the liquid is filled last.

3.5.5 *On-line powder fill followed by off-line liquid fill* – This method is similar to that in 3.5.4, except the liquid is added to the containers after they have been removed from the line. The medium can be added to the containers manually in either the same fill suite or an entirely different aseptic processing area. When the liquid medium is added to the powder-filled containers in a separate aseptic processing area, the containers must be sealed prior to removal from the powder fill area, and their exterior surfaces sanitized upon introduction into the other aseptic processing area. The closures then are removed manually, the liquid medium introduced and the containers resealed. The use of isolation technology for performing the off-line liquid addition is recommended.

Advantage(s)

None; extensive non-routine manipulations added to the aseptic filling process.

Disadvantage(s)

Increased manipulation of containers.

Second filler to set up and validate.

3.5.6 *Non-aspetic liquid fill, sterilized and followed by on-line powder fill* – For this method, liquid-filled units (filled either manually or automatically outside the aseptic processing area) are steam sterilized, open, in an autoclave. The sterilized units are unloaded in the aseptic processing area onto the filling line for powder addition.

Advantage(s)

None; facility limited.

Disadvantage(s)

Manipulation of open containers increases the potential for contamination unrelated to the powder fill process.

Sterilization of open containers in autoclave must be validated.

3.5.7 *Off-line liquid fill followed by on-line powder fill* – An off-line liquid filler is utilized in the aseptic processing area for filling of the vials which are then transferred to the powder filling machine.

Advantages(s)

None; facility limited.

Disadvantage(s)

Transfer of open containers is not part of the routine powder filling process and increases contamination potential.

Second filler to set up and validate.

3.5.8 *Special considerations unique to the simulation of aseptic fillling of sterile powders*

Negative Controls – With the exception of the method in 3.5.1, all of the dry powder process simulation test procedures entail the filling of both a sterile liquid and a sterile placebo powder. It is common to fill some number of containers solely with liquid, for use as negative controls. The intent of this liquid fill procedure is to confirm that the liquid fill system is not the source, should the combined fill demonstrate contamination. The liquid units generally are filled before starting the powder fill. This assures that if the liquid filler cannot be operated successfully, the remainder of the fill is canceled.

Negative liquid controls are not required, but may be performed at the firm's discretion. This would be possible where the firm has a history of success with liquid

fills using the same equipment. The absence of negative controls on the liquid fill may create some problems in failure resolution, but offers advantages in reduced numbers of units filled.

Where negative controls are used, the detection of contamination in any of the control units invalidates the results of the simulation.

3.6 Other Dosage Forms

This document presents validation approaches for the more common sterile dosage forms. There are other, less common dosage forms, e.g., inhalants, aerosols and implants which are produced. The paucity of available data on process simulation testing for these dosage forms necessitated their exclusion from this document. The concepts provided herein can be used as a guide to the development of a validation program suited for the particular requirements of these dosage forms.

3.7 Advanced Aseptic Processing Technologies

There are two major advances in aseptic processing technology which currently are undergoing extensive study. Form-fill-seal and isolation technology both offer several operational advantages over conventional clean rooms for the production of aseptic products. These technologies provide enhanced environments in which the processes described in this document may be performed.

The reader is strongly cautioned to consider the following two sections as preliminary estimates of appropriate limits and follow developments on these technologies as new information becomes available.

3.7.1 *Form-Fill-Seal and Blow-Fill-Seal* – The medical device industry, primarily in the area of eye care products, and, to a lesser extent, the parenteral industry are implementing form-fill-seal and blow-fill-seal systems for the filling of aseptic solutions. Process simulation test results have been reported by numerous practitioners in the literature, citing contamination rates far lower than those observed with conventional aseptic filling. These technologies lend themselves to long runs covering many thousands of filled units, sometimes well in excess of 100,000. At the present time, a maximum contamination rate of not more than one contaminated unit in 15,000 units seems routinely attainable with this technology (1-3).

3.7.2 *Isolation Technology* – Isolation technology holds great promise in the area of aseptic manufacturing and filling. It already has been implemented in a number of facilities, and numerous others are under active consideration or installation. Given the relative novelty of the technology and the limited number of fully operational systems, identification of performance criteria for process simulation testing is somewhat premature. The goal in these systems is to eliminate personnel intervention, maximize the level of asepsis and substantially increase the sterility assurance level. Where isolator systems are operated as sealed environments, a design objective of zero contamination for the process simulation test, regardless of the size of the trial might be considered. For isolator systems operated in an open manner with continuous discharge of components, limits somewhat tighter than those suggested for conventional aseptic processing should be considered (4-6).

NOTE: Comments about isolators relate only to systems which can be sterilized while sealed, and operated either open or closed. When operated closed, they may exchange air with the surrounding environment through HEPA filters; open, air may be discharged to the environment through a "mouse hole." The comments are not appropriate for "barrier systems" which cannot be sterilized while sealed.

4. DOCUMENTATION

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

4.1 Process Definition

The first step is to define the process to be simulated. The process is defined as all steps from the sterilization of the drug substance, excipients if present, container and closure, to the point the drug product is sealed. The maximum time frames for storage of the sterile drug container and closures prior to aseptic assembly must be factored into the simulation.

4.2 Protocol Preparation

Once the process has been clearly defined, the simulation protocol or procedure can be written. This document should include but not be limited to the following information:

- Identification of the process to be simulated
- Identification of the room to be used
- Identification of the filling line and equipment to be used
- Type of container/closure to be used
- Line speed
- Number of units to be filled
- Number and type of interventions and stoppages to be included in the simulation
- Number of personnel participating
- Media to be used
- Volume of medium to be filled into the containers
- Incubator identification, and incubation time and temperature for the filled units
- Environmental monitoring to be performed
- A copy of the batch record to be used
- Acceptance criteria for all the tests performed
- Description of the documentation required for the final report
- Rationale for the "worst case" parameters chosen
- Box or tray number of any positive unit(s)
- Growth support testing requirements and result

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.

4.3 Protocol Execution

Execution of the protocol is performed through the batch record. The batch record gives detailed instructions on how to perform the process simulation test. It should be written in the same format as a normal batch record and contain all the normal data and sign-off elements. All information which normally would be attached to a batch record also should be attached to the simulation batch record, i.e., cleaning and sterilization records for pieces of equipment used, release stickers for the containers and closures etc. All interventions, planned or unplanned, and stoppages must be documented in the batch record as to the type of intervention, time the intervention occurred, duration of the intervention or stoppage and the number of the box or tray being filled. The last step is to document the following:

- Number of units filled
- Number of units incubated
- Number of units positive
- Number of units rejected for cause (damaged container, defective seal)
- Growth promotion of medium (after incubation)

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

5. MICROBIOLOGICAL ENVIRONMENTAL MONITORING

A carefully planned and executed microbiological environmental monitoring program provides increased assurance of sterility for aseptically prepared products by demonstrating that environmental conditions conducive to the production of sterile product are constantly being met and by assuring that appropriate systems and utilities are functioning as intended.

In accordance with CGMP requirements, microbiological environmental and personnel monitoring should be carried out during process simulation testing, using routine operating procedures. This must include the set-up period and, specifically, set-up personnel.

Details concerning elements of an effective microbiological monitoring program, including sample site selection, sample frequency, alert and action levels, methodology and interpretation of data, can be found in PDA Technical Report No. 13, "Fundamentals of a Microbiological Monitoring Program," Supplement S, *Journal of Parenteral Science and Technology,* Vol. 44, 1990.

Microbiological environmental monitoring data collected during process simulation tests often are used to help establish and support initial environmental monitoring action levels for normal aseptic processing area operations.

6. ELEMENTS OF PROCESS SIMULATION TESTS

This section contains important general information to consider when conducting any type of process simulation test. Issues such as fill volumes, line speeds, container sizes and run duration play a key role in effectively simulating the production process.

The following parameters should be considered when developing a process simulation test program. The advice is derived largely from the PDA 1992 survey on aseptic processing (7).

6.1 Set-Up

The filling line set-up usually entails manual assembly of the equipment. Equipment set-up activities may require more manipulation of critical surfaces than subsequent filling operations. The process simulation test should be designed to detect potential contamination from set-up activities.

6.2 Interventions

Process simulation tests must include all the normal activities which occur during an aseptic filling process (i.e., weight adjustments, container-closure resupply etc.) in order to substantiate the acceptability of those practices in routine operation. It is possible that non-planned interventions may be necessary to correct for container breakage, fluid leakage, closure jams etc., which may occur during the process simulation. 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 correctable during an ordinary fill. Some firms have chosen to videotape process simulation tests for the express purpose of documenting random events (i.e., container breakage, tip-over of a container, stopper jam etc.), and demonstrating their ability to correct these problems successfully.

6.3 Container Size

In general, process simulation trials will entail the filling of the largest and smallest containers on a given filling line. Exceptions to this general rule occur when the same filling machine, on the same filling line is used for very different product presentations. In these instances, the flexibility of the filler may make it necessary to test more than one set of large and small containers, because the filling set-ups are so different. For new facilities, two fills utilizing the largest container and a single fill of the smallest container appear to be the preferred initial trials; subsequent periodic fills would alternate between the sizes.

6.4 Container/Closure Configuration

When a particular container/closure configuration provides unique operating challenges (e.g., tipping, jams etc.) and causes increased interventions, it is recommended a separate process simulation test be performed with that particular configuration. Clear containers of identical configuration may be substituted for opaque or

amber containers to aid in the detection of contamination.

6.5 Filling Speed

In general, the fill speed to be used for any container should be set at the low end of the filling speed range for that size container. If higher speed results in the potential for greater interventions, that speed should be considered when selecting process simulation test parameters.

6.6 Fill Volume

There continues to be consensus that the container need not be filled to its normal fill volume. Where partial fills are employed, the fill speed should follow the advice given in Section 6.5. Regardless of the actual fill volume, the process simulation test should include a fill weight adjustment using methods identical to those employed during production. While the exact amount of medium utilized in a partial fill is not critical, there are two general criteria. First, there must be enough medium in the container to contact all the container-closure seal surfaces when the container is inverted and swirled. Second, there must be enough medium in the container to allow for the detection of microbial growth.

6.7 Duration of Fill

Process simulation tests should be of sufficient duration to allow enough containers to be filled to properly determine the contamination rate. Normal aseptic manipulations such as initial set-up activities, adjusting fill weights or volumes, changing equipment and manual maintenance operations should be included in process simulation tests.

Process simulation tests also should be of sufficient duration to include a representative number of atypical interventions which might occur during an actual production filling operation. Where they are part of normal operations, gown changes, breaks and shift changes should be simulated. A process simulation test fill size of 3,000 to 5,000 units generally is sufficient to demonstrate acceptable process control for conventional aseptic filling operations. However, for certain high speed filling operations, it might be necessary to fill more units in order to accommodate normal aseptic manipulations and intervention events. (See section 6.2)

6.8 Production Batch Size/Process Simulation Test Size

Concerns over the proper size of a process simulation test in relation to the size of the production batch require a different answer for each range of batch size (in the following subsection, N refers to the routine *production* batch size). The need to incorporate routine interventions in the process simulation test may result in an increase in the number of medium-filled units from that indicated below.

6.8.1 *Large Batch Size* – N > 100,000 units – For these types of processes, where high speed fillers are commonplace, it might be possible to fill 3,000 units in less than five minutes. If this practice were followed, the process simulation test would bear little resemblance to the normal production operation. These large batch sizes may necssitate filling more than 3,000–5,000 units in order to accommodate the number of interventions normally used in production. Process simulation testing for large batches can be carried out in different ways. Among these methods are:

—Fill 3,000 units with medium, switch to sterile WFI for an extended period of time, fill an additional 3,000 units with medium.

—Fill 3,000 units with medium, simulate filling (components are replenished and processed through the equipment) for an extended period of time, fill an additional 3,000 units with medium.

—At the completion of a regular production batch, disassemble the line and reassemble with sterilized equipment, then fill 3,000 units with medium.

—After an extended WFI fill, disassemble the line and reassmble with sterilized equipment, then fill 3,000 units with medium.

—Simulate filling for an extended period of time, disassemble the line and reassemble with sterilized equipment, then fill 3,000 units with medium.

6.8.2 *Conventional Batch Sizes* – 100,000 > N > 3,000 units – For these types of processes, the number of units to be filled with medium can approach the size of the actual production batch, especially with the trend toward larger and larger process simulation tests. Current practice appears to indicate that many firms are performing such tests with a minimum of 3,000 units.

6.8.3 *Small Batches* – 3,000 > N > 1,000 – For this batch size, which might be common for a clinical batch or other developmental situation, the minimum process simulation batch size should be equal to the standard maximum batch size. While this does not afford the level of statistical confidence frequently associated with process simulation tests, it is a reasonable compromise, given the limitations of the batch size.

6.8.4 *Very Small Batches* – 1,000 > N – For batches of this size, which are common in certain clinical and radiopharmaceutical operations, a process simulation test at the maximum batch size is recommended. Forcing the production of 3,000 or even 1,000 units may produce situations so different from the normal operation that the results may be meaningless. For simulation of these batch sizes, the process simulation test must evidence no growth in any of the filled containers to be acceptable.

NOTE: Where batch sizes are small, the incidence of fully manual filling operations is more prevalent, and the reader is encouraged to review the discussion on that subject presented in section 6.9.

6.9 Manual Filling

When the batch size is small, there is a greater prevalence of manual filling for the preparation of sterile products. In the least automated of these situations, an operator will place the container under the

filling needle, apply a closure and then manually seal the container. There are a number of variations to this process in which some portion(s) of the process are carried out semi-automatically or automatically. Nevertheless, the degree of manual manipulation of sterile surfaces is greater in this form of process than would occur in any machine fill procedure. The validation of a manual process of this sort is carried out in accordance with all of the methods and practices outlined in this section, with one significant addition. Each operator who performs this type of manual filling should be individually evaluated in multiple trials to establish the acceptability of his aseptic technique. In essence, each operator is treated as an individual sterile filling system, and therefore requires individual evaluation.

6.10 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.

6.11 Media Selection

The most common medium for process simulation testing is Soybean-Casein Digest Broth. In special circumstances, the use of a second medium may be necessary.

6.12 Media Growth Promotion

The medium itself should be capable of supporting a wide range of microorganisms. Generally, the medium is prepared according to manufacturer's recommendations, but adaptations might be needed to accommodate such processing steps as partial lyophilization, reconstitution of powder fills, increased viscosity of certain formulations etc. The medium should be sterilized by the same process (e.g., steam sterilization or sterile filtration) as the drug product it represents. In the case of filtration, it may be difficult to process the rehydrated medium identically to the drug due to differences in solubility characteristics. It may be necessary to try several manufacturers of the dry base powder, due to variations in blending/milling among manufacturers, or it may be necessary to insert a pre-filter(s) in line. In extreme cases the medium may be diluted to half or quarter strength to enhance sterilization by filtration. Should it become necessary to insert additional filters or dilute the medium, the effect on the ability of the medium to support growth should be evaluated.

Finally, the medium should be growth tested. Samples may be tested initially upon production. They also may be tested concurrent with incubation and/or after 14 days of incubation. The units used for growth testing must be subjected to the same processing steps (e.g., cleaning, depyrogenation, sterilization, filtration, filling, lyophilization, reconstitution) up to the point at which they are placed into incubation. The medium's growth properties should be evaluated using pharmacopeial methods, and the inclusion of environmental organisms or those isolated from sterility test positives may be beneficial.

6.13 Container Inspection

The containers should be inspected for any breach of integrity which may have gone undiscovered during release inspection prior to incubation, or could have occurred during post-inspection handling (e.g., transport to incubator, microbiological inspections). This integrity check should be quick, simple, non-intrusive to the container unless already adulterated, and cause no damage to the organisms in the container.

The units should be examined visually for evidence of growth. Containers should be manipulated during the inspection process to ensure detection of contamination on container and closure surfaces. In some instances, it may be advisable to inspect containers midway through the incubation period. These incubator checks should be performed by personnel who have had specific training in the visual inspection of media-filled units. Any positives noted during routine inspection should be tallied and immediately removed from incubation.

Damaged containers should not be considered in the evaluation (acceptance) of the aseptic processing capability of the process. If the number of positives obtained exceeds the allowable level, refer to Section 8 – Failure Investigation and Corrective Action.

If the container is not integral, the source of the breach should be investigated and corrective action taken. The corrective action may include: a change in release inspection procedures; retraining of line inspectors; different containers used to transport and hold media units; or retraining of microbiology inspectors, depending upon the cause of the breech. An identification of the organism may be performed, but the information will most likely be of little value for damaged containers.

6.14 Inert Gassing

Where sterile inert gases are used during normal production, process simulation tests should substitute sterile air. The sterility of the inert gas system is confirmed through filter validation and integrity testing, not by means of the process simulation test. The use of an inert gas with Soybean-Casein Digest Medium may inhibit growth. If it is necessary to use an inert gas, testing should confirm the ability of the inert gas/medium combination to support microbial growth. (See also Section 3.2.4.3)

6.15 Facility Considerations

The organization of a process simulation test program for even a modest sized facility involves additional considerations compared to a single fill operation. Firms must address the validation of multiple fill rooms, and the use of the same fill room or filling machine for different types of processes. The general approach is to assure that all aseptic filling operations are evaluated on a semi-annual basis. That may necessitate multiple process simulation tests in a given room to address all the permutations of aseptic processing which take place there. The key consideration is that it is the aseptic filling process which is being evaluated, and not a specific room or machine. If a process is sufficiently different from the others in the room or on the machine, then a process simulation test at six-month intervals should be performed.

6.16 Staffing Considerations

Each person who works in an aseptic filling suite should participate in a successful simulation test on a periodic basis. Firms have addressed this expectation by maintaining logs of personnel who have participated in each fill as part of the documentation. However, participation only is not enough; the operators must perform the same tasks they would perform in the execution of a normal fill. Similarly, each of the set-up operators should be qualified to confirm their competence in aseptic assembly on a set-up for each type of filling process they perform.

A frequent consideration is the performance of aseptic filling on a second, or even third shift. In these instances, the filling operation may continue for an extended period of time. It is expected that the process simulation test program will address this type of operation.

7. INTERPRETATION OF RESULTS AND ACCEPTANCE CRITERIA

7.1 Background

The question of limits and acceptance criteria invariably evokes debate among experts. How many units constitute a valid process simulation test (media fill)? How many positives should be allowed? Should the limit be a set number or should it be statistically derived from process capability studies and environmental monitoring results? How should high speed lines and long duration runs be handled? Should all potential interventions be addressed during each process simulation test, or should a few be introduced during each run and the sum total reviewed over time? Can statistics be used to justify a high number of positives for large process simulation tests, e.g., eight positives out of 16,000 filled units?

Despite the number of units filled during a process simulation test or the number of positives allowed, the ultimate goal for the number of positives in any process simulation test should be zero. A sterile product is, after all, one which contains no viable organisms.

There are, however, numerous technical problems in achieving this goal. Media and simulated product do not match real products perfectly in terms of their processing characteristics and microbiological growth support properties. 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 powdered products, the process simulation test involves reconstituting powdered media or simulated product, introducing extra processing equipment or manipulation, with the inherent risk of contamination. Since a microbiological medium is designed specifically to support or stimulate the growth of microorganisms, it is a more rigorous challenge than processed products, which often provide neutral and sometimes hostile microbial growth environments. Thus, a limit of some low number other than zero often is chosen.

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.

7.2 Strategies

The validation of aseptic processing has been a subject of considerable discussion within the parenteral industry since the mid-1970s. Many individual authors, industry associations, compendial bodies and regulatory agencies have seen fit to define the practices, methodologies and key concepts to be included in this activity (8–13). The contributions from these various sources have shaped current industry practice.

Several divergent approaches may be used. One method is to apply the contamination rate as an absolute value and accept an established percentage (e.g., 0.1%) of the filled units, without regard to the number filled. A second procedure is to employ a full statistical approach for process simulation tests, regardless of the number of units filled, with a confidence level.

The recommended procedure, however, is to establish acceptance criteria appropriate for the processing technology incorporating the firm's operating experience. Lacking sufficient operational data, firms may wish to set initial acceptance criteria based upon industry surveys, e.g., *PDA Technical Report No. 17, Current Practices in the Validation of Aseptic Processing – 1992,* modifying those limits when sufficient operational experience has been achieved.

NOTE: PDA intends to survey industry practices in this area periodically. The latest survey available should be used to identify current practices.

7.3 Guidance

The following guidance may be used to establish appropriate process simulation test limits and acceptance criteria:

- The test methodology must simulate the process as closely as possible.

- Rationale for the chosen methodology and limits must be justifiable and documented.
- Test methodology should be sensitive enough to confirm a low process simulation test contamination rate, and the selected limit must be routinely achievable.
- Any positive unit indicates a potential problem, regardless of run size. All positives should be identified and should result in a thorough, documented investigation.
- Process simulation test contamination rates approaching zero should be achievable using automated production lines in well-designed aseptic processing facilities, blow-fill-seal and form-fill-seal and in isolator-based systems (1–6).
- Processes conducted in older facilities or employing considerable product handling or manual operation may not be capable of achieving near-zero contamination rates. Nevertheless, such processes must be capable of a process simulation test contamination rate not exceeding one in 1,000 when 3,000 units are filled (11).
- For batch sizes smaller than 3,000 units, process simulation tests should at least equal the batch size. No positives should be allowed due to the low sensitivity of small runs.
- When more than 3,000 units are filled, caution should be used when deciding to increase the allowable number of positives based on arithmetic extrapolation.

8. FAILURE INVESTIGATION AND CORRECTIVE ACTION

A contaminated container should be examined carefully for any breach in the integrity of the container system. Damaged containers should not be considered in the evaluation (acceptance) of the aseptic processing capability of the process.

All positives (from integral containers) should be identified to at least genus, and to species whenever possible. A comprehensive consistent sampling and identification scheme is crucial in the investigation and determination of the contaminant source. In the instance when the process simulation test does not meet the established acceptance criteria, all possible sources of contamination should be investigated. A detailed history of the investigation needs to be maintained.

The identity of microorganisms from the contaminated units should be determined. The identification of the contaminant should be compared to the database of the organisms recently identified. The biochemical (genus/species) profile of the contaminating microorganisms can then be compared to that of microorganisms obtained from the sterility tests and bioburden and environmental monitoring programs, in order to help identify the potential sources of the contaminant. These isolates should be checked for possible identification matches, as should isolates for any areas which exceed their count limits or are trending upward. In addition, literature references detailing possible sources of the organism may be helpful in locating its point of entry into the process.

Processing records should be reviewed. If the process simulation test was monitored/videotaped, the records/tapes should be reviewed for any deviations from accepted procedures. A batch production record similar to that for routine production should exist for each process simulation test. Any deviations, down times and repairs before or during filling should be noted. Filter integrity testing results and all sterilization records associated with product components and equipment should be examined. Cleaning and sanitization records should be reviewed.

Critical systems (HVAC, compressed air/gas, water, steam) should be reviewed for documented changes and requalification or acceptance criteria for those changes. Calibration records should be checked. All HEPA filters in the filling area should be inspected and recertified, if warranted. Training records for all individuals (production, maintenance, cleaning) involved in the fill should be reviewed to assure proper training was provided.

Validation records can be reviewed for any procedure or process changes. All deviations from the original validation should have an associated justification for not performing a new validation.

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.

The failure investigation report should contain:

- A summary of the occurrence
- All systems investigated, not just the systems tied to the failure
- A conclusion as to cause(s) and supporting documentation
- Potential effect on previous batches produced
- Corrective action(s) taken
- Outcome of additional process simulation tests, if performed
- Appropriate signatures. In addition to the signatures of the investigators of the individual systems, the overall report should be signed by the heads of Production and Quality

The investigation needs to be completed in a timely fashion. It may be necessary to issue an interim report, with anticipated time lines, if the investigation or corrective actions require excessive time.

NOTE: This section is not intended to be all inclusive. Additional elements may need to be added depending upon the process.

9. VALIDATION MAINTENANCE

Each firm should determine the frequency of and interval between periodic reassessment of each process. A six-month interval between process simulation tests is widely accepted in the pharmaceutical industry.

There may be several different permutations of a filling process which take place on a given filling line. If these processes differ significantly, then supporting process simulation tests should be performed for each process. In such cases, one approach may be to perform process simulation tests for these processes on a rotational basis, with each process challenged at least annually. Depending upon individual circumstances, however, more frequent process simulation testing may be necessary.

Performance of process simulation tests prior to the scheduled reassessment may be necessary following a process change of such scope that previous qualification studies would be invalidated. In such cases, the number of process simulation tests may vary, depending uponthe extent of the change. Examples of such changes include:

- Major modifications to the equipment or immediate product containers/closures (interchanging standard parts does not constitute a major equipment modification)
- Modification to equipment or facilities which potentially affects the air quality of airflow in the aseptic environment
- Major changes in the number of production personnel or initiation of second (or third) shift production when the facility has been qualified only for single shift operations
- Major changes to the aseptic production process and/or procedures

It also may be necessary to requalify with acceptable process simulation tests in response to adverse trends or failures in the on-going monitoring of the facility or process, such as:

- Continued critical area environmental monitoring results above the alert/action levels
- An increased incidence of product sterility test failures
- Breach of asepsis in the aseptic processing area

When such incidents occur, the process and any changes which may have occurred since the previous qualification should be evaluated. Appropriate action can then be taken to restore the facility or process to its "qualified state." Process simulation testing may be appropriate to assure that the "qualified state" has been re-established.

APPENDIX 1
SELECTION AND STERILIZATION OF PLACEBO POWDER MATERIALS

In the conduct of aseptic process simulation tests for suspensions, ointments, creams and dry powder fills, the use of a sterile placebo powder is commonplace. 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. It may be possible to use sterile dry powdered medium in the process simulation test, however its utility may be hindered by the fineness of the powder and poor handling characteristics. Whichever material is used as a placebo, it should be packaged identically to the sterile powder being simulated.

Selection of Placebo Powder – The selection of placebo material for use in process simulation testing must consider several factors. The seemingly obvious choice of dry sterile media, itself, has proven less than successful because of its poor flow properties, which make its passage through conventional powder handling equipment or a typical sterile powder filling machine a considerable challenge. The principal placebo materials which have been used successfully are lactose, mannitol, polyethylene glycol 6000 and sodium chloride. 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 mock formulation processes or easily filled in the powder filling equipment.

Sterilization of Placebo Powder – 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 a final container, generally a heat sealed plastic bag, identical to that used for sterile powders. Alternatively, the material can be sterilized by gas, dry heat or even by 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 of the Placebo Powder – Growth promotion testing, in which the chosen material is tested for potential inhibition, is performing using *Bacillus subtilis* and *Candida albicans.* Consideration should be given to testing with other microorganisms commonly found in the aseptic processing area environment, such as those isolated during personnel monitoring and sterility test contaminants. The sterilized placebo material is dispersed in sterile WFI, and added to sterile medium at a range of concentrations approximating that to be utilized in the process simulation test, typically 1.0–5.0%. Replicate samples at each concentration are inoculated with 10–100 CFU of each of the challenge organisms. Positive controls are prepared by inoculating replicate tubes of medium which do not contain the sterilized placebo powder. Growth must be evident in all tubes within seven days after incubation at 20–25° C.

Solubility Testing of the Placebo Powder – The solubility of the placebo powders at the desired concentration is determined in the test medium. The amount of agitation required to solubilize or disperse the powder, as well as the time and degree of solubilization should be noted. If the powder fails to dissolve or disperse fully, it can be retested at a lower concentration or replaced.

APPENDIX 2
DEFINITIONS

Action level (environmental monitoring)
Established criteria, e.g., microbial or particulate levels, requiring immediate follow-up and documented corrective action if exceeded.

Action plan
A written plan of elements to be accomplished to achieve a specific result, including responsibility for each element and target date for completion.

Aerobic organisms
Microorganisms which utilize oxygen as the final electron acceptor during metabolism; microorganisms which will grow only in the presence of oxygen.

Alert levels (environmental monitoring)
Established microbial or particulate levels giving early warning of potential drift from normal operating conditions, which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

Anaerobic organisms
Microorganisms which do not utilize oxygen as the final electron acceptor during metabolism; microorganisms which will grow only in the absence of oxygen.

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.

Barrier system
A processing system which provides for some measure of separation between the critical zone and operating personnel. It is not hermetically sealed nor sterilizable.

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

Colony forming unit (CFU)
Visible outcome of growth of microorganisms arising from a single or multiple cells.

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

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, and includes a corrective action plan when 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 filter system.

Isolator, closed
A sealed and sterilized enclosure which provides total separation between one environment and another except for air exchange, which takes place through HEPA filters.

Isolator, open
Similar to a closed isolator, except that air can leave the pressurized enclosure through an open conveyor port or "mouse hole." It can be sterilized when this opening is closed.

Microbiological identification
Biochemical characterization of isolated colonies to determine the isolates' genus and, where feasible and appropriate, species.

Process simulation test
Method of evaluating an aseptic process using a microbial growth medium.
NOTE: Process simulation tests are understood to be synonymous with media fills, simulated product fills, broth trials, broth fills etc.

Positive
Test sample which exhibits detectable microbial growth after incubation.

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

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.

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.

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

1. J. Sharp, "Manufacture of sterile pharmaceutical products using 'blow-fill-seal' technology," *The Pharmaceutical Journal*, **239**, 106 (1987).
2. J. Sharp, "Validation of a new form-fill-seal installation," *Manufacturing Chemist*, p. 22, February (1988).
3. A. C. Kvarnström, L. Ernerot and K. Mattsson, "Form-Fill-Seal: Experience with the Aseptic Filling and Terminal Sterilization of Small Volume Parenterals," *Proceedings of PDA International Congress*, **180** (1992).
4. L. Edwards and M. Porter, "Microbiological and Physical Limits Testing of a Locally Controlled Environment (LCE) Prototype Filling System," *Proceedings of PDA/ISPE Conference on Advanced Barrier Technology* (1995).
5. M. Sweeney, S. Davenport and L. Edwards, "Validation Issues for a Production Barrier/Isolator Sterile Liquid Filling System in a Controlled Environment," *Proceedings of PDA/ISPE Conference on Advanced Barrier Technology* (1995).
6. W. Frieben and R. M. Enzinger, "Capabilities of Advanced Aseptic Processing," CDER and FDA Small Business Conference on Aseptic Filling, October 12–13, 1993.
7. "Technical Report No. 17, Current Practices in the Validation of Aseptic Processing—1992," *J. Par. Sci. Tech.*, **47** (S1), PDA (1993).
8. "Annex 4, General Requirements for the Sterility of Biological Substances, Part A, Section 2," World Health Organization (1973).
9. "Technical Monograph No. 2, Validation of Aseptic Filling for Solution Drug Products," PDA (1980).
10. "Technical Report No. 6, Validation of Aseptic Drug Powder Filling Processes," PDA (1984).
11. "Guideline on Sterile Drug Products Produced by Aseptic Processing," FDA (1987).
12. "Technical Report No. 13, Fundamentals of a Microbiological Environmental Monitoring Program," *J. Par. Sci. Tech.*, **44** (S1), PDA (1990).
13. "Technical Monograph No. 4, The Use of Process Simulation Tests in the Evaluation of Processes for the Manufacture of Sterile Products," The Parenteral Society (1993).