

Managing Aseptic Interventions

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This article outlines a comprehensive approach for organizing a firm's aseptic operations, including planning for routine and nonroutine interventions, establishing effective process simulations, and determining which vials to incubate.

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Performing an aseptic process almost always requires operators to manipulate sterile or sterilized products and components. These activities are universally considered to offer the greatest potential for introducing microbial contamination (1–4). That potential has been recognized by the US Food and Drug Administration inspectors and has led to some substantial concerns raised in warning letters issued in 2000 (5–6). The measures taken to respond to these concerns by the companies involved have implications for other firms performing aseptic processing. The PDA held a conference call in November 2001 with representatives of the Office of Compliance at FDA's Center for Drug Evaluation and Research (CDER) to address relevant issues and establish some ground rules for the industry to follow. Participants in that conversation were Joseph Famulare and Richard Friedman of FDA, and Edmund Fry, Russell Madsen, and the author, who represented PDA. The essence of that conversation was subsequently reported in the PDA newsletter (7).

This article outlines a comprehensive approach for organizing a firm's aseptic operations consistent with the results of that discussion and aligned with recently defined regulatory expectations. The approach was initially developed in the spring of 2000 to suit the specific needs of a major manufacturer of aseptic products and subsequently was refined through application in a variety of settings at other firms.

Human interventions in aseptic processing

It is appropriate to focus on human interventions performed during aseptic processing because no other factor has the same potential for introducing contamination. Sterilization processes, environmental sanitization, room design, and heating and ventilation systems are all substantially less significant as sources of contamination. Personnel continuously shed microorganisms and particles to their surroundings and gowning materials cannot contain the millions of organisms present on human skin. The proximity of personnel and thus substantial numbers of potentially contaminating microorganisms to sterile materials, components, and surfaces during the performance of interventions is largely unavoidable in staffed cleanrooms.

Routine and nonroutine interventions. Interventions in aseptic processing operations fall into two main categories: routine and

nonroutine. *Routine interventions* are activities that are inherent parts of the aseptic process and integral parts of every batch. Typical routine interventions include:

- aseptic assembly of the equipment before use;
- initial product connection or introduction;
- start-up component supply or introduction;
- initial fill weight or volume adjustment;
- periodic component replenishment;
- periodic fill weight or volume checking and verification;
- fill weight or volume adjustment;
- environmental monitoring;
- operator breaks and meals;
- operator shift changes;
- product sampling;
- filter integrity testing;
- product container replacement;
- component change (different sizes);
- fill-volume change;
- any other interventional activity which is an integral part of the process.

Nonroutine interventions are activities that are predominantly corrective and may not be a part of every batch. Although in theory, nonroutine interventions may not be necessary during the aseptic process, in practice such interventions are almost always required to correct some anomaly. Some common non-routine interventions involve:

- stopper misfeeds or clumping;
- fallen, broken, or jammed containers;
- defective seals on containers;
- product spillage or leakage;
- product filter change;
- sensor adjustments or replacement;
- filling needle replacement;
- fill-pump replacement;
- stopper bowl changes;
- timing adjustments;
- conveyor or guide rail adjustments;
- any other line malfunction requiring manual correction.

The perfect intervention

In aseptic processing, the perfect intervention is the one that is not required. The fewer the interventions, the lower the likelihood of contamination. Reducing the number of interventions should be the goal in every aseptic process. Operators should strive for this goal throughout the operational life of the process. Interventions can be eliminated by at least three major means: process and procedural design, improving component quality, and process automation.

Process and procedural design. Process and procedural design elements that can reduce interventions include eliminating interventions by performing clean-in-place and sterilize-in-place procedures for the filling assembly; removing samples after process materials have been transferred; eliminating unnecessary sampling steps; and using the pressure-hold method for filter integrity verification to obviate the need for a downstream connection.

Improving component quality. Interventions also can be eliminated by improving component quality. Examples include es-

tablishing tighter acceptable quality levels for containers, seals, and other parts that must be assembled; and ensuring better control over component preparation to provide greater operational consistency.

Process automation. Human intervention also can be reduced by automating processes. Examples include robotic sampling for fill weights, servo-adjustable fill volumes, automated removal of downed containers, and automated stopper seal integrity testing.

Another way to reduce the number of interventions is to encourage operators to examine the necessity of an intervention before performing it. For example, a vial that has fallen over on a turntable should be left on its side until it presents a problem feeding other containers. If no problem occurs, the fallen vial will still be on the turntable at the completion of the fill, thereby eliminating the intervention entirely.

Identifying interventions

Looking at the list of interventions provided above, it might appear that a firm need only address those items. That approach may be insufficient, however. The preferred approach is to assemble the operating personnel and have each operator develop a list of routine and nonroutine interventions. For firms with multiple aseptic operations, interventions may vary one from fill line to another, even if both are filling similar products and containers. Variations in product type may add activities that are specific to individual situations. The initial goal of this activity is to compile a list of all interventions for each circumstance.

The next step is to review the interventions with the operating personnel and supervisory staff to ensure appropriateness and consistency of terminology. In the course of the dialogue, certain interventions may be deleted from the list because they present an unacceptable contamination risk. Then, each intervention should be discussed in detail and a preferred means for executing the intervention should be identified—although two or more operators may have identified the same intervention, they may not perform it in an identical or even fully acceptable manner. A competent microbiologist familiar with aseptic technique should participate in this process. Once agreed upon, each intervention (whether routine and nonroutine) should be established within a single standard operating procedure for each fill line, process, or product type. This SOP should be applied to both process simulations and routine operations.

The procedures must include sufficient detail to eliminate ambiguity. For example, because many interventions require the removal of containers or components from the line, the extent of removal must be exact. For instance, an SOP might indicate that when clearing a stopper jam, the operator should remove three containers on either side of the container under the track where the jam occurred. Whenever possible, the numbers of components to be removed during each intervention should be identified and that number should be consistent for simulation and production.

In some instances, it may be preferable to define the extent of removal by location rather than number. The procedure might state, “remove all open containers between the last fill

head and the stopper machine,” rather than, “remove the six open containers between the stopper machine and the last fill head.” If the conveyor happens not to be full between those locations, requiring the removal of six vials may cause confusion and lead to inconsistent execution of the task.

Training personnel to execute the interventions is of paramount importance. Each person who is expected to perform

an intervention in routine operation must become proficient in its execution. The preparation of a video depicting the proper methods for each intervention is highly recommended because it can be extremely difficult to convey in words the proper method for performing an intervention. If the intervention methods are identical for all operators, questions regarding operator participation will be re-

duced. Thus, the intervention procedure becomes qualified regardless of which operator performs it. If a firm has many operators, this alignment of procedures can help simplify the process simulation program. When new operators are introduced into the operation, the approved intervention procedures become a major focus of their task-specific training.

Process simulation of routine and nonroutine interventions

Because routine interventions are integral and necessary parts of every aseptic process, their execution during process simulation should occur at the same frequency as in an ordinary aseptic production process. Fortunately, this is relatively easy to accomplish. The setup of the line for the process simulation should follow essentially identical procedures to those used for production. The only differences might be using air instead of nitrogen for blanketing or purging (to enhance recovery of potential microbial contaminants) and adapting in-line polishing filters to maintain flow rates. The remaining routine interventions are either prescheduled by procedure (e.g., weight checks or adjustments) or occur at regular intervals (e.g., component replenishment). By requiring the aseptic simulation to follow practices identical to those used for routine production, routine interventions will be performed at the same frequency in both, thus ensuring that the simulation is a valid representation of the routine process.

Nonroutine interventions vary substantially from routine interventions. Nonroutine interventions occur randomly during the process in response to faults. The frequency with which they occur may vary substantially as a result of factors outside our knowledge or ability to control. To ensure their correct execution during routine operations, these interventions must be included in process simulations at a realistic frequency level.

Nonroutine interventions should not be optional in simulations. If operators do not practice nonroutine interventions during simulations, the operators will be unable to perform those interventions during actual aseptic production.

The suggested means for integrating nonroutine interventions into a process



simulation is to schedule them as if they were integral to the process, at approximately the same frequency with which they occur during normal operations. The operators should perform the non-routine intervention following the approved procedure as closely as possible. The media fill observer (whose presence is strongly recommended during every process simulation) must ensure that

nonroutine interventions are executed correctly.

Routine and nonroutine interventions in routine operation

Interventions that occur during routine operations should be performed using the methods that have been established as SOPs and practiced during process simulation studies. Occasionally, however,

something may occur during an aseptic process that requires an intervention that was never considered or that was considered to present a unacceptable level of risk. The process should be terminated at that point. Unless an intervention has been fully integrated into both the process simulation and routine operational setting, no assurance exists that it can be performed without introducing contamination. No intervention should be permitted unless it has been satisfactorily accomplished in at least one media fill. If the need to perform an unapproved intervention occurs with increasing frequency, the firm should take corrective measures to alleviate or eliminate the situation. If appropriate, the firm can add interventions to its approved list, provided those interventions are incorporated into the process simulation program.

It is important to document in the batch records all nonroutine interventions that are performed during both process simulation and routine filling. The documentation should include the time the intervention was performed and its identification (using a number system can minimize recordkeeping). Because routine interventions are an integral part of the production process, documenting their execution is already part of the production record system. Batch record review allows supervisory staff to monitor operations and determine whether a particular intervention is becoming frequent enough that corrective measures are required. Tracking the nonroutine intervention frequency allows the firm to develop its process simulation program to support the more-common nonroutine interventions in every process simulation and relegate those that are less frequent to a longer interval between simulations.

Which units to incubate?

All process simulations include three populations (see Figure 1). Population 1 represents marketable product and consists of fully acceptable units with integral container-closure and units with cosmetic defects that ordinarily would be removed during post-fill inspection. Population 2 consists of intervention units removed by procedure or practice during the course of the fill. Any units that are automatically sorted out of the batch by the equipment



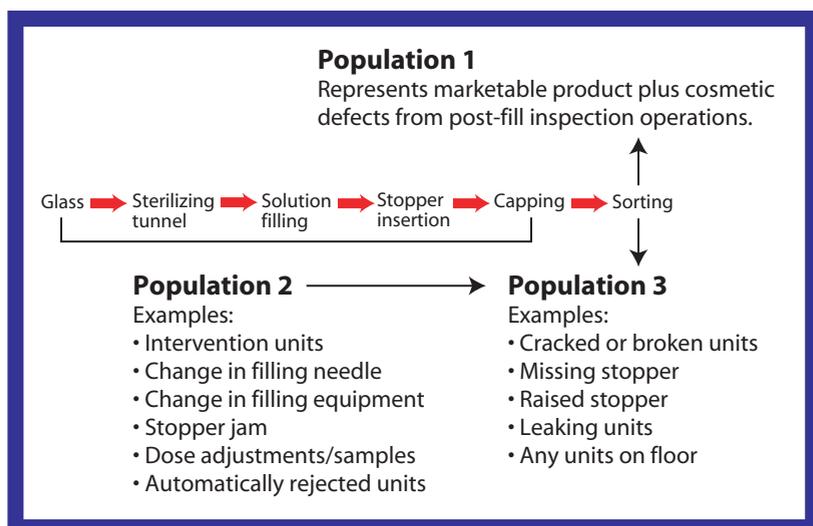


Figure 1: The three populations that occur in all process simulations.

during processing would also be included in Population 2. Population 3 consists of any unit with compromised container-closure integrity that would be culled from the fill during the pre-incubation inspection.

After the completion of a process simulation, filled units must be carefully inspected before incubation to eliminate containers with compromised integrity, because only units that are rep-

resentative of marketable product should be incubated.

This means that only Population 1 should be incubated. Units removed from the filling process, either as part of an intervention during the media fill (*i.e.*, Population 2) or after the fill is completed (*i.e.*, Population 3) should be discarded. The majority of these units will be unfilled, unsealed, or uncrimped. Manually sealing and crimping these units is not a part of routine operations because it is likely to introduce contamination. Little benefit will be gained from testing such vials. Detecting contamination in the removed units does not imply contamination of the overall aseptic process; the presumption of contamination that prompted their removal in the first place suggests that any

contamination detected in those units would not be representative of the remaining units.

All containers in Population 1 must be included in the statistical evaluation of the media fill. No containers can be disregarded once they have been incubated. This population represents marketable product and vials with cosmetic defects that should be removed in post-filling inspection. The cosmetic defects are included in Population 1 because their removal during a production batch is subject to the vagaries of the cosmetic in-



spection process, and thus they are potentially representative of marketed product.

Incubating any remaining media that was not filled into containers may be useful, but certainly is not required. If that media is heavily contaminated, it might invalidate the entire fill. However, if the residual media is contaminated but the filled units are free of growth, then the results of the fill must stand. In effect, the

presence of growth in the residual media has little relevance to the media fill, except in those instances where it results in the failure of the media fill, which ordinarily is considered a non-test, requiring that the test be repeated.

Conclusion

When intervention practices are detailed in procedures used in an identical man-

ner for both process simulation and routine operation, the adequacy of the aseptic process can be demonstrated by successful media fills. Aligning the intervention procedures eliminates the uncertainties associated with varying practices and supports the successful execution. Incubating the units removed during processing provides no additional assurance—these units are always rejects during either production or process simulation. Incubating nonintegral containers is an exercise in folly. Process simulations are assessments of aseptic processing capability and are not definitive determinations of sterility assurance. Inferences that not-incubated units evidencing contamination are indicative of aseptic process failure represent a biased viewpoint.

References

1. J. Agalloco and B. Gordon, "Current Practices in the Use of Media Fills in the Validation of Aseptic Processing," *J. Parenteral Sci. Technol.* **41** (4), 128–141 (1987).
2. J. Agalloco and J. Akers, "Current Practices in the Validation of Aseptic Processing—1992," *J. Parenteral Sci. Technol.* **47** (2), supplement (1993).
3. J. Agalloco and J. Akers, "Current Practices in the Validation of Aseptic Processing—1996," *PDA Technical Report 24, PDA J. Pharm. Sci. Technol.* **51** (2), supplement (1997).
4. J. Agalloco and J. Akers, "Current Practices in the Validation of Aseptic Processing—2001," *PDA Technical Report 24, PDA J. Pharm. Sci. Technol.* **56** (3), supplement (2002).
5. Food and Drug Administration, Warning Letter to Alcon Laboratories, 17 November 2000, www.fda.gov/foi/warning_letters/m4877n.pdf (accessed 18 February 2005).
6. Food and Drug Administration, Warning Letter to Eli Lilly & Co. Inc., 2 March 2001, www.fda.gov/foi/warning_letters/m5257n.pdf (accessed 18 February 2005).
7. PDA, *PDA Newsletter*, February 2002.
8. US Food and Drug Administration, *Draft Concept Paper on Sterile Drug Products Produced by Aseptic Processing* (FDA, Rockville, MD, September 2002). **PT**

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