



# Concept Paper Discusses Update of Aseptic Processing Guidelines

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The recently issued FDA concept paper about aseptic processing shows how the current guidelines could be expanded and makes recommendations for alternatives to traditional cleanroom installations such as isolator-equipped aseptic filling lines and blow-fill-seal equipment.

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Fifteen years have passed since FDA published guidelines for aseptic processing. During those years, technology advanced rapidly, and the number of products being aseptically processed grew substantially. Isolator-equipped filling lines also evolved into an alternative to traditional cleanrooms.

In an effort to meet the expanding needs of today's pharmaceutical manufacturers, FDA has been working

to update its guidelines for aseptic processing, and it finally issued a concept paper on 27 September 2002. The much-anticipated draft document, "Sterile Drug Products Produced by Aseptic Processing," has been the talk of the industry ever since.

At approximately 50 pages, this concept paper is considerably longer than the existing guidelines that were issued in 1987. It also takes a more risk-based management approach, a strategy the agency has been adopting in other areas, including revisions of CGMPs. New subjects include guidance for personnel qualification, cleanroom classifications under dynamic conditions, room design, quality control, environmental monitoring, and reviews of production records, isolators, and blow-fill-seal systems.

Other sections feature a lengthy discussion of container-closure preparation and inspection, endotoxin control, process validation and equipment qualification, batch-record review for process-control documentation, and laboratory controls. The latter includes topics such as process simulation, filtration efficacy, sterilization of equipment, and containers and closures.

Concluding the work are several related appendices. The first focuses on aseptic processing isola-

tors, which have gained a strong position among parenteral drug makers during the past decade. The second discusses blow-fill-seal technology, and a third describes processing before filling-sealing operations. The concept paper concludes with lists of references and relevant guidance documents followed by a glossary that defines approximately 30 terms related to aseptic processing.

What has not changed is FDA's stance that "sterile drugs should be manufactured by aseptic processing only when terminal sterilization is not feasible." To find support for this policy, one need look no further than the years between 1980 and 2000 when nearly all of the recalls for nonsterility or lack of sterility assurance involved aseptically processed products.

Reaction to the long-awaited draft has been generally favorable, although some concerns and modifications have been suggested in comments submitted to the agency. Considerable discussion also ensued at a day-long meeting organized by the Parenteral Drug Association (PDA) on 9 December 2002, during which attendees emphasized the importance of familiarizing FDA field personnel with any new guidelines to ensure consistent treatment from inspector to inspector.

Comments submitted by PDA's ad hoc Subcommittee on Aseptic Processing comprise four main subject areas: numbers and limits, media fills, environmental monitoring, and sterility testing.

**Numbers and limits.** The subcommittee advocates building flexibility into the guidelines to accommodate advancing technology and the individual procedures followed by various companies, and it notes that any numbers and limits stated in the guideline should be supported by scientific data. This approach is particularly necessary for microbial control limits because, according to the subcommittee, "standard sample collection and microbiological methods for these environmental tests have not been defined." The comment letter proceeds to explain that "in actual practice, it is extremely difficult to establish microbial limits that are statistically valid. For example, FDA suggests a limit of one viable organism per 10 cubic feet of air. However, there is no reason to believe that a finding of two or three or-

## FDA's concept paper emphasizes system integrity and maintenance.

ganisms per cubic foot on a single sample would indicate that product quality had been jeopardized.”

**Media fills.** Requirements for media-fill tests also should be flexible, according to the subcommittee. Such tests shouldn't be given undue significance because they don't necessarily provide an improved level of quality assurance in operations with appropriate environmental control, produc-

tion supervision, and operator training practices.

**Environmental monitoring.** The subcommittee also maintains that environmental monitoring should focus on critical sites rather than on critical surfaces because many of the critical surfaces listed “are inaccessible ... or not readily sampled ... without jeopardizing the quality of the material being filled.”

**Sterility testing.** The sterility testing section of the subcommittee's comment letter discusses the choice of methods, media, personnel, sampling and incubation, and investigation of sterility positives. Although the PDA subcommittee's comments are quite detailed, the group makes the following basic points:

- Sterility-test problems should be addressed in the compendia.
- The investigation of a first-stage failure will in most cases not be definitive.
- Microbial identification data may not reliably establish the source of a contaminant.
- The technical limitations of sterility tests are not adequately discussed.

Because so much confusion exists about the interpretation of sterility-test results, PDA's Research Committee is conducting a survey to determine how industry responds to evidence of a first-stage failure.

### Aseptic processing isolators

Unlike the 1987 guidelines document, the 2002 concept paper addresses isolator technology, whereby the filling line is enclosed in a controlled environment rather than set up in a cleanroom. The agency states that a well-designed isolator system “appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing.” It also warns that “users should not adopt a ‘false sense of security’ with these systems,” and adds that “manufacturers should also be aware of the need to establish new procedures addressing issues unique to these systems.”

FDA's concept paper emphasizes system integrity and maintenance as well as regular replacement of items such as gloves, half-suits, seams, gaskets, and seals, which, if breached, can allow contamination into the system. Gloves, which typically are mounted to allow operators to manipulate items inside an isolator enclosure without breaking the seal,

should be inspected at every use. "The choice of durable glove materials coupled with a well-justified replacement frequency are two aspects of good manufacturing practice that should be addressed," the paper states. In addition, "due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly, and the operator should also wear a second pair of thin gloves."

Appendix A also reiterates FDA's contention that isolators should not be located in unclassified rooms. "A Class 10,000 or Class 100,000 background is appropriate depending on isolator design and manufacturing situations."

The concept paper's overview of decontamination procedures includes several requirements:

- Written procedures for decontamination should be established.
- The decontamination process must fully expose all surfaces to the sterilant. To ensure that this happens, glove fingers should

be separated and fully extended during the decontamination cycle.

- Decontamination cycles should include an extra margin of kill time to ensure that viable microorganisms are eliminated.
- Biological indicator (BI) challenges should be used to validate the decontamination process. "For most production applications, demonstration of a six-log reduction of the challenge BI is recommended," the paper states.
- Decontamination should be completed according to a validated schedule or whenever a breach in isolator integrity occurs because of a power failure, glove/seam tear, air leak, loss of pressure, or other problem. "Breaches of integrity should be investigated, and any product that may have been impacted by the breach should be rejected."

Other isolator requirements that are described in the paper include the establishment of an environmental monitoring program to periodically check the microbiological quality of air, surfaces, and gloves and monitoring of particulate levels in the interior and at the exit port.

Finally, because human operators generally pose the biggest contamination threat to an isolator-based system, "meticulous aseptic technique standards must be observed."

### Blow-fill-seal technology

Appendix 2 of the FDA document acknowledges the advantages that blow-fill-seal technology offers. A system that forms, fills, and seals containers in a controlled environment demonstrates economies in container-closure processing as well as reduced human intervention. However, equipment must be designed to control the particulates generated by the plastic extrusion, cutting, and sealing processes. Process monitoring and environmental monitoring are particularly important. FDA states that "samples should be taken during each shift at specified locations under dynamic conditions." Continuous monitoring of particulates can help control the system.

Companies that use blow-fill-seal systems must ensure that containers are sterile and nonpyrogenic. In addition, "the plastic polymer material chosen should be pharmaceutical grade, safe, pure, and pass USP criteria for plastics. Polymer suppliers should be qualified and monitored for raw-material quality." In addition, each sealed container should be inspected to identify and reject any problem containers such as leakers.

FDA concept papers are not binding to either the agency or industry. However, it is likely that this document, with some revisions based on industry comments, will form the foundation for any future guidelines related to aseptic processing. **PT**

### FYI

#### Updated resource available

The updated and revised *Standard for the Use of the International System of Units (SI): The Modern Metric System* is available from the American National Standard for Metric System (ASTM). The 69-page document provides information that defines and comments on SI quantities and units used to describe such properties as mass, force, weight, temperature, pressure, angle, moment of inertia, and kinetic energy. Rules for conversion and rounding and various easy-to-understand tables are included.

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