



## Revising the 1987 Industry Guideline

# The Development of FDA's Guidance on Aseptic Processing

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FDA, led by CDER's Office of Compliance, is developing its guidance document regarding aseptic processing to update the 1987 industry guideline "Sterile Drug Products Produced by Aseptic Processing." The authors describe the solicitation of industry input for the guidance through a process that included a 2002 meeting of the Advisory Committee on Pharmaceutical Science and the subsequent formation of the PQRI Aseptic Processing Working Group. The working group obtained input from 50 aseptic filling facilities and data for 600 individual media fills. The working group's recommendations will be considered in the development of this CGMP guidance by FDA.

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**O**n 27 September 2002, FDA released a concept paper regarding aseptic processing. This concept paper (available at [www.fda.gov/cder/dmpq](http://www.fda.gov/cder/dmpq)) is essentially a working revision of the 1987 industry guideline entitled "Sterile Drug Products Produced by Aseptic Processing," which was issued jointly by the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA) (1). FDA's overarching goal is to provide a document that will facilitate industry compliance. The agency's focus is on the critical control points of sterile processing and risk-based CGMP systems. Ultimately, the final guidance will provide greater clarity by including updated information regarding CGMP expectations for aseptic processing facilities, highlighting the latest scientific developments in this area of sterile drug quality.

The original aseptic processing guidance document was published 16 years ago. Because of the complexity involved in aseptic processing and to reflect the evolution of science and new technology in this area, FDA felt that it would be beneficial to solicit early input before formal issuance of a draft revision for public comment. Accordingly, the publication of the concept paper not only provided an unprecedented opportunity for a preview of our current thinking but also allowed us to obtain feedback, both formal and informal, regarding the content of the revised guidance.

## Launching of the concept paper

A meeting of the Advisory Committee for Pharmaceutical Science was held on 22 October 2002, during which the concept paper was discussed in a public forum and critiqued by the committee as well as a panel of invited aseptic processing experts. Representatives of industry and technical organizations presented at the meeting. These included PhRMA, PDA, GPhA, the PDA isolator technology task force, independent consultants, academia, and pharmaceutical companies. Members of CDER, CBER and ORA delivered several introductory presentations, all of which emphasized a risk-based approach. The use of a risk-based approach to applying CGMP requirements is a major theme of FDA's "Pharmaceutical CGMP for the 21st Century" initiative (2). This initiative encourages manufacturers to adopt modern, innovative manufacturing technologies and to use existing and emerging science to identify and control critical factors that may affect process dependability and product quality (3). In addition to providing a framework for developing a more useful guidance for the industry, this approach is helping FDA use its resources effectively and apply regulatory and manufacturing standards consistently.

A number of critical factors should be taken into account when designing an aseptic facility. The concept paper focuses on contamination risk areas, including facility design and maintenance, equipment qualification, sterilization and depyrogenation operations, disinfection practices, personnel, and strict adherence to aseptic procedures during production (4,5).

At the advisory committee meeting, there was consensus regarding the urgent need for FDA to publish updated guidance on aseptic processing. The industry provided positive feedback about the agency's interest in promoting advancements in technology such as aseptic processing isolators. For example, the concept paper states the following on the topic of positive-pressure isolators:

An emerging aseptic processing technology uses isolation systems to minimize the extent of personnel involvement and to separate the external cleanroom environment from the aseptic processing line. A

well-designed positive-pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing.

Because isolators have now established a favorable track record, one editing suggestion was to remove the word *emerging* from this section. The authors share this opinion because isolator technology is no longer a new or emerging technology. The industry at large has installed isolators of sound design, and they afford an improved level of product protection.

At the advisory committee meeting several issues were identified as areas requiring further discussion and for which a firm consensus was sought. Some of the issues were matters of refining word choice and others required more thorough analysis and discussion. For example, media fills, environmental monitoring, isolators, and disinfection were all identified as areas that require additional scientific input.

## PQRI Aseptic Processing Working Group

One of the recommendations from the Advisory Committee for Pharmaceutical Science was to form a working group under the Product Quality Research Institute (PQRI) to address key issues of industry concern. PQRI has also sponsored other recent projects among industry, academia, and FDA. We believe that PQRI is a particularly good venue for such discussion because of its emphasis on data-driven analysis and its science-based focus on regulatory issues. The new working group was composed of 41 aseptic processing experts from industry, academia, and FDA. After meeting with the PQRI steering committee to define the objectives of the new aseptic processing working group, the PQRI working group members then met frequently over a three-month period, conducting extensive discussions about the scientific and practical merits of specific aseptic processing concepts. A major component of the PQRI project was to collect data about current aseptic processing practice and capabilities. In December 2002 a questionnaire covering several topics, accompanied by a spreadsheet survey about

various aspects of media-fill practices, was posted on the PQRI Web site with links from the FDA, PDA, and AAPS Web sites. PQRI received responses from 50 aseptic filling facilities and data from more than 600 individual media fills. The PQRI working group completed 8 specific text clarifications on the concept paper and 10 detailed recommendations on various aspects of aseptic processing. Each of the 10 PQRI recommendations offers multiple technical points for FDA to consider when it prepares the draft guidance for public comment.

The PQRI working group completed this task on 10 March 2003, arriving at consensus positions for each of the issues. The PQRI steering committee forwarded the working group's final report to FDA on 19 March, and it was subsequently posted on PQRI's Web site ([www.pqri.org](http://www.pqri.org)) (6). The group resolved many issues, including two particularly controversial ones:

**Parameters for determining the number of units needed for a media-fill run.** The working group agreed that the number of units to be filled should be sufficient to accurately simulate activities that are representative of the manufacturing process. A media fill should be large enough to adequately simulate the interventions that occur in a given aseptic processing operation. The size of a media-fill run also will depend on the contamination risk of the manufacturing process, on the basis of whether it is highly manual, automated, or conducted in an isolator. Specific numerical starting points also are provided in the report.

**Critical surface sampling.** The working group endorsed the principle in the concept paper that states that critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during production. It outlines a rationale for determining which critical sites are the most useful to monitor in an environmental monitoring program. The selection of sample sites in environmental monitoring should be based on contamination risk and each site's relationship to the process. An infrequent positive result at a critical site should not necessarily result in batch rejection. Trend analysis (both intra- and inter-day) for these

and other environmental results normally provides the most meaningful insight into environmental control.

## Conclusion

Our interaction with PQRI has involved vigorous and challenging discussions, and the process has been worthwhile and fruitful. FDA ultimately came to consensus on major issues identified by PQRI and the Advisory Committee for Pharmaceutical Science that have for many years been inadequately articulated for both the industry and FDA. The PQRI working group worked collegially and arrived at conclusions that were based on science, data from industrial practices, and the application of risk-assessment concepts to product quality.

FDA's next step is to consider the recommendations from PQRI in revising the concept paper. It is our intention that our proactive efforts and direct interactions with industry and academia will facilitate a more efficient public comment process and prompt publication of the final guidance.

Following the consideration of comments from both PQRI and the advisory committee, the revised concept paper will be published as draft guidance for public comment. This public comment period will provide further opportunity for all interested parties to submit their comments to FDA as the process for finalization of the guidance moves forward. One theme has pervaded our efforts throughout this revision process: The agency is reaching out to the various constituents involved to maximize feedback. We plan to continue participating in conferences to engage in open dialogue about practical experiences and the latest scientific knowledge. Our ultimate goal is to publish an updated, useful industry guidance as rapidly as possible. We believe the risk-based approaches used in rewriting the guidance will facilitate better understanding of CGMP as a reflection of the current science relating to sterile drug quality.

## Disclaimer

These comments are those of the writers only and do not necessarily represent the positions or policies of FDA.

## References

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