

# The Future of Aseptic Processing—An Update

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In spite of regulatory uncertainties, the industry continues to develop improved aseptic processing technologies.



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Last year I wrote in these pages about the future of aseptic processing. At that time the industry was waiting for FDA to publish a replacement for its 1987 “Guideline on Sterile Drug Products Produced by Aseptic Processing” and wrestling with issues such as media-fill acceptance criteria, interventions and intervention management, environmental monitoring practices and acceptance levels, rapid microbial methods, sterility test insensitivity, regulatory harmonization, and how best to implement, control, and monitor improved aseptic processing technologies such as isolators and barrier systems.

Much has changed in a year, yet much remains the same. In September 2003, FDA published a revision to its 1987 aseptic processing guidance, a draft entitled, “Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice.” September was also the effective date for small but significant changes to the EC Guide to Good Manufacturing Practice, Annex I, “Manufacture of Sterile Medicinal Products.” Revisions to these guidance documents touched off waves of commentary and controversy on both sides of the Atlantic, prompting industry trade groups, professional associations, companies, and individuals to convene, discuss the implications of the changes, and submit numerous comments to FDA and EMEA. Relatively unchanged, however, is the uncertainty regarding the regulatory acceptability of aseptic processing practices such as environmental monitoring and intervention management, as well as isolator decontamination and the use of fraction-negative calculations to measure its efficacy.

Although much remains to be accomplished, the revised guidance documents have clarified regulatory positions in several important areas, including media-fill acceptance criteria and air classification levels for viable and nonviable particulates.

Nonetheless, this increased clarity fails to resolve the continued lack of harmonization and the technical problems caused by new, impractical requirements such as the directive in EC Annex 1 to sample 1 m<sup>3</sup> of air in grade A and B areas for 5- $\mu$ m particles and the requirement in the FDA guidance to classify the aseptic processing environment under dynamic conditions.

FDA and EMEA have committed to addressing these and the other issues that engendered significant comment. If they follow through as promised, the resulting guidance documents will be practical, scientifically based, and internationally harmonized.

In spite of the regulatory uncertainties, the industry continues to develop improved aseptic processing technologies based on minimizing human intervention. One promising new method involves filling sterile liquid into presterilized, sealed vials in an isolator by injecting the liquid through the stopper, then immediately laser-sealing the resulting puncture. High-throughput isolators and barrier systems continue to be developed and refined. These technologies hold the promise of producing aseptically processed products that have the same sterility assurance levels as products that are terminally sterilized.

The articles in this second *Aseptic Processing* supplement to *Pharmaceutical Technology* paint a comprehensive picture of the issues affecting the continued growth and success of aseptic processing. The articles cover interventions and intervention management, environmental monitoring, new and rapid microbial methods, process simulations, isolation technology, airflow measurement and control, critical analysis of the FDA draft aseptic processing guidance, and adopting a risk-based approach to aseptic processing.

What will another year bring? Undoubtedly uncertainty, but unquestionably progress! **PT**