

Perspectives on Aseptic Guidance

A Critical Review of FDA's 2003 Draft Guidance and a Proposed Alternative

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FDA's draft guidance on aseptic processing contains some inherent difficulties, including **unrealistic expectations of sterility and microbial quantification, an absence of harmonization with international rules,** and failure to support new technologies or a risk-based approach. The authors propose a science-based alternative.

The need for new regulatory guidance regarding aseptic processing has engendered significant debate and controversy. Many individuals want key expectations to be clearly defined and numerical requirements standardized in the hope that FDA inspectors will enforce the guidance with a great deal of uniformity. Others believe flexibility of implementation is required and prefer guidance that provides broad examples but clearly supports alternative approaches.

The draft guidance issued by FDA in September 2003 seems to satisfy neither group. It endeavors to satisfy both constituencies and unfortunately fails in the attempt. In this article, we have not attempted to provide a line-by-line commentary. The official comment period for the draft aseptic processing guidance closed on 4 November 2003, and FDA is now considering the submitted comments. Our goal here is to critically review the draft guidance at the conceptual level and highlight some of the more difficult and controversial elements. We also propose what we believe is an effective alternative to an aseptic processing guidance document. In doing so, we hope to outline important issues, clarify critical concerns, and in the process educate FDA and the industry.

Critical review

The excerpts from the draft guidance presented below reflect many of the difficulties inherent with the guidance, but we have not addressed many other problems. The comments we have personally submitted to FDA are extensive and not limited to the content of this paper. (Note: Excerpts from the draft guidance are shown in quotation marks and italicized. Line numbers are from the PDF version of the draft.)

Expectations of sterility

"Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants." (Line 152)

"Air monitoring of critical areas should normally yield no microbiological contaminants." (Line 214)

"Critical surfaces that come in contact with the sterile product should be sterile." (Line 1166)

The guidance document frequently mentions the need for "sterility" within the environment used for aseptic processing. Of course, it would be ideal to attain a "sterile" state in which

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to conduct aseptic processing; however, attaining that goal is an impossibility. Because personnel are present in manned cleanrooms and perform all of the activities, including microbial sampling, the attainment of the condition of sterility is unrealistic. Since it is not possible to operate a staffed cleanroom in a sterile condition, it is also unrealistic to expect product contact surfaces within an aseptic environment to be demonstrably sterile. The detection of microorganisms in these environments on an occasional basis is inevitable, and their recovery at a normal frequency should not be cause for extreme countermeasures nor for action against the product. Even the absence of personnel from the operating areas (as found in an isolator) cannot ensure a “sterile” condition in which to conduct the aseptic process.

The draft guidance addresses “false negatives” in sampling, yet it fails to adequately consider the more likely possibility of “false positives.” It also fails to objectively consider measurement capability and uncertainty in microbiological environmental assessment. Aseptic sampling is an operator activity prone to the same uncertainties as any other human intervention, and it must be recognized that perfection is not achievable. In the context of the guidance document, the only meaningful results are those used to cast suspicion on the process. Scientifically, however, a positive result should carry no more weight than a negative one when evaluating the “sterility” of the aseptic environment.

Expectations regarding microbial quantification

“... and scientifically sound methods.” (Line 1152)

“... although all allow a quantitative testing of the number of organisms per volume of air sampled.” (Line 1257)

“Because devices vary, the user should assess the suitability of all monitoring devices before they are placed into service.” (Line 1264)

The draft guidance consistently suggests that microbial monitoring is a precise measurement of the actual number of organisms present in an environment. This position is not unique to this draft, and many documents pertaining to aseptic processing, including international guidelines, have taken a similar stance. Nevertheless, implying that sterility can be measured is scientifically incorrect. In fact, conventional microbiological assessment is so prone to variability that the implication that accurate measurement can be attained with any degree of certainty is inappropriate. Given the inability of microbial sampling apparatus to be “calibrated” or “standardized” in the sense that other, nonmicrobial sampling systems can be, precise microbial quantification is impossible. Yet this guidance document makes accurate measurement of low levels of microorganisms a requirement in every aseptic processing operation. Distinguishing between microbial counts of <10 cfu per sample implies a precision in sampling and recovery that is unrealistic. Differences among the various active microbial sampling systems also will result in variations from the idealized results and expectations suggested in the guidance.

Expectation of dynamic classification

“... the final room or area classification should be derived from data generated under dynamic conditions ...” (Line 134)

“All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.” (Line 146)

The draft guidance recommends that aseptic processing environments be classified under dynamic conditions (i.e., with all systems operating, components and personnel present). This is a practical impossibility. Facilities are conventionally classified under static conditions as stated in all other environmental classification systems (i.e., ISO 14644, FS 209, USP 1116, and EU Annex 1). The impact of factors outside the control of the facility designers and cleanroom classification contractors relating to microbial control, gowning practice, and operator technique preclude classification in an operating mode. In addition, the classification of environments has been largely restricted to particle control; classification schemes that include microbial limits are far more problematic because a fixed relationship does not exist between the number of nonviable and viable particles present in the various environments.

Absence of harmonization

“Averaging of results can mask unacceptable localized conditions.” (Line 1205)

The averaging of results from environments is an expectation of EU Annex 1. Section 5 explicitly states, “These are average values.”

“Settling plates lack value as quantitative air monitors because only microorganisms that settle onto the agar surface will be detected.” (Line 1270)

The use of settling plates is recommended in EU Annex 1 and is a useful adjunct to the short sampling periods associated with many active microbial sampling systems. The suggestion that they are less than a useful means of microbial evaluation reveals a bias toward practices in the United States, where their use is less common.

The sterile products industry operates on a global scale and many large firms have developed “centers of excellence” in which products are manufactured for global markets in a single facility. Many small firms have limited sourcing capability and must produce all of their output for worldwide supply at a single operating facility. Harmonization is an economic reality today, and regulations should embrace it whenever possible. The guidance document doesn’t harmonize with either EU Annex 1 or the ISO 14644 series. FDA requirements are different numerically and preclude averaging of results as required in the EU Annex 1.

Failure to embrace improved technologies

“However, a leak in any of certain components of the system can constitute a significant breach of integrity.” (Line 1547)

“A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity.” (Line 1556)

“Induction can result from local turbulent flow causing air swirls or pressure waves that can push extraneous particles into the isolator.” (Line 1604)

“A decontamination method should be developed that renders the inner surfaces of the isolator free of viable microorganisms.” (Line 1654)

Appendix 1 of the guidance addresses isolator technology, yet it leaves the clear impression that this technology requires more control and monitoring than conventional, staffed cleanrooms. Several statements made in this appendix raise the suspicion of a problem with isolators, where comparable cleanroom practices are even less secure. If FDA’s goal is to improve the safety of aseptically produced products, then its treatment of isolators should be supportive of the technology. It has been shown that processing in isolators is superior in all respects to aseptic processing in staffed cleanrooms. To impede their further adoption, as has certainly been the case in the United States relative to Europe and Japan, is inappropriate and risks public health. Isolators do not have to be perfect to aseptically produce sterile products with greater confidence than is attainable in any staffed environment.

Absence of scientific support

“The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within a defined space.” (Line 198)

The note at the bottom of the page cites values abandoned in Fed-Std-209C in 1987. The velocity requirements cited as footnote 4 date to 1972. Cleanroom experts effectively abandoned the need for a narrow air velocity range in the 1970s in favor of velocities based on evaluation of the requirements of the particular cleanroom configuration and process, because they considered the narrow air velocity range irrelevant to the maintenance of the classified environments.

“The characteristics of these agents generally preclude the reliable use of statistical methods (e.g., fraction negative) to determine process lethality.” (Line 1657)

Fraction-negative studies can be an important element of cycle development for gas decontamination procedures. To establish an exposure period, fraction-negative studies are perhaps the best possible method. Their use as justification for positive results when a negative is expected (or even required) is a misuse of the science and is not reason to disavow an extremely useful technique.

“... and at a defined distance proximal to the work surface for HEPA filters in the critical area.” (Line 331)

Monitoring of air velocity in this manner lacks precedent and its relevance to the performance of the air system over the critical area is unknown. Its imposition as a “requirement” without reference, methodology, and supportive rationale is inappropriate.

The draft guidance contains many speculative opinions that are scientifically unsupportable (except in some cases by out-

dated references). To venture far from accepted scientific principles reduces the guidance’s effectiveness. When guidance is given that is not based on scientific fact, firms essentially are forced to implement scientifically inconsistent practices, an unfortunate and often expensive situation. In a few cases, the guidance draws on older (and obsolete) references to maintain outdated perspectives inconsistent with what are now well established facts.

Overly ambitious scope

“In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility confidence.” (Line 114)

Sterilization of Equipment and Container and Closures (Lines 1029–1133)

Sterility Testing (Lines 1339–1498)

Aseptic Processing Isolators; Design (Lines 1568–1583)

The document includes brief coverage of subjects such as sterilization, sterility testing, and isolator design. Some of these subjects (e.g., sterilization, sterility testing) have been more fully addressed elsewhere, whereas others (e.g., isolator technology) are so new in concept that the guidance provided is deficient, incorrect, and/or misleading. Because these subjects are somewhat peripheral to the key subject, they should be mentioned in passing or not at all.

Failure to support a risk-based approach

“... increased scrutiny (e.g., extra supervision, monitoring) of the production process should be implemented.” (Line 775)

“In the absence of any adverse trend, a single result above an action level should trigger an evaluation and a determination about whether remedial measures may be appropriate.” (Line 1182)

“An in-process limit for bioburden level for each formulated product (generally sampled immediately preceding sterile filtration) should be established.” (Line 1318)

“the batch processing circumstances—samples should be taken in conjunction with processing interventions or excursions.” (Line 1395)

“... whether utility and/or support systems (e.g., HVAC, WFI) are functioning properly.” (Line 1489)

The draft guidance consistently adds requirements to aseptic processing operations that are not in widespread use, which is not aligned with FDA’s announced initiative, “Pharmaceutical CGMPs for the Twenty-First Century: A Risk Based Approach.” Because there is no evidence suggesting that a public health concern currently exists for aseptically produced products, these additions serve little purpose and in some instances the added requirements could actually increase the risk of contaminated product.

The nonscientific nature of these sections of the guidance inhibits innovation and process improvement and raises unnecessary compliance concerns in areas that have no impact on product safety. The number of unrealistic cautionary statements made regarding isolators will undoubtedly slow the implementation of this superior technology that has the potential to replace the more risky staffed cleanroom.

A proposed alternative

The draft guidance establishes a goal of excellence in aseptic processing, a goal that is shared by the industry and all who work in it. However, it presents a vision of operating requirements that is currently unattainable. Aseptic environments cannot be made into “sterile areas”; no cleanroom, environmental monitoring program, or media fill result could accomplish that. Even isolators, the current pinnacle of aseptic processing capability, cannot be considered “sterile.” The tenor of the guidance document suggests that perfection in performance should be attainable on a daily basis. As a goal, perfection in aseptic processing is certainly an acceptable target; however, as an operational requirement as defined in this draft guidance, it is inappropriate.

Guidance for aseptic processing must accept the real limitations that are faced when products are manufactured using methods that do not involve terminal sterilization. The formalization of impractical aseptic guidance will result in controversy and regulatory problems. The guidance must allow for flexibility of practice, especially if it is to avoid restricting technology.

Perhaps the greatest flaw in the draft guidance is its treatment of isolator technology. Isolators are addressed with a skepticism that belies their operational superiority over staffed cleanrooms. The industry is cautioned, “However, users should not adopt a false sense of security with these systems.” Are we somehow expected to feel more confident using manned cleanrooms than isolators? We hope not. Isolators have the potential for producing sterile products aseptically and with a higher degree of confidence than perhaps any other current technology. Risk can be further reduced as automation, robotics, and other technical advances are incorporated into isolator technology. The way forward is a risk-based regulatory process rather than a punitive approach or an approach based on fear. The consumption of enormous human and financial resources in the conduct of validation work that has little bearing on risk mitigation does nothing but slow the implementation of technology and increase risk to the end user.

We believe industry prefers science-based guidance that unambiguously presents FDA’s requirements for aseptic processing systems and controls. Such guidance must be comprehensive and reasonably specific, avoiding terms such as “adequate,” and “as appropriate.” It also must be flexible enough to address the varieties of scale and technology inherent in aseptic processing today. However, because specificity and flexibility are conflicting conditions, any new aseptic processing guidance document is unlikely to cover both.

We also believe that the Offices of Regulatory Affairs (ORA) and Compliance require guidance that ensures conformity with CGMPs and is flexible enough to allow for evolving technology and regulatory expectations. The Office of Pharmaceutical Science requires guidance that provides reviewers enough flexibility to accommodate the “it depends” responses that are often required when answering questions such as where and how air flow measurements should be taken in the aseptic processing area critical zone.

How can these seemingly contradictory requirements be resolved? We propose a strategy consistent with the Preapproval

Inspection program and FDA’s 1994 “Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products.” This is how it would look:

- FDA would revise the Guidance for Industry document referenced above to expand the existing template containing the requirements for information and documentation to be submitted in an application for aseptically processed products. This information would include environmental monitoring procedures as well as media fill practices, interventions, and acceptance criteria.
- Firms would develop and submit specific information unique to their aseptic processing practices and controls according to the template.
- The application would be reviewed and approved according to existing procedures.
- ORA would inspect each firm or site according to the approved filing, rather than against the general aseptic processing guidance document.
- To accommodate advances in technology, firms would be required to update the manufacturing controls section of the application on a periodic basis. This could be a change being effected (CBE) or CBE 30 or preapproval filing (minor/moderate/major). FDA would not be authorized to open the application to review other areas.

The proposal might require a change in regulatory policy, but we believe it would provide an ideal mechanism for providing aseptic processing guidance for the following reasons:

- The proposal improves regulatory alignment with chemistry, manufacturing, and controls requirements in 21 *CFR* 314.50(d)(1) and restores the regulatory authority described in Food, Drug, and Cosmetic Act 505(b)(4)(G).
- It is aligned with FDA’s “Pharmaceutical CGMPs for the Twenty-First Century: A Risk-Based Approach” initiative.
- The proposal provides all stakeholders the specificity and flexibility needed to produce and regulate aseptically produced products.

This proposed approach to managing aseptic processing activities was developed by a group of concerned individuals and submitted in writing to the Center for Drug Evaluation and Research in April 2003. We support this approach and believe it is a strategy that is in keeping with both the process analytical technologies (PAT) and CGMPs for the twenty-first century initiative.

Whatever the outcome (guidance alone or something else), it must be practical, scientifically grounded, internationally harmonized, and aligned with FDA’s risk-based CGMP and PAT initiatives. Once this is achieved, the result will be improved understanding of the scientific issues pertaining to aseptic processing and an atmosphere in which technological advancements and innovations not only are possible but are encouraged and nurtured, thereby benefiting regulators, industry, and most important, the patients who rely on aseptically produced medicines to ensure their continued health and well-being. **PT**