Aseptic Processing: A Review of Current Industry Practice

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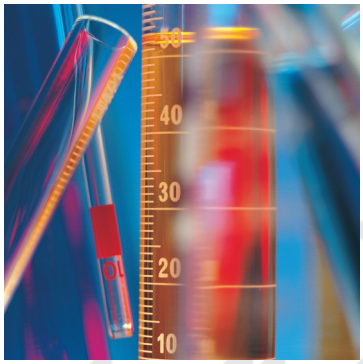

DIGITAL VISION

This article reviews current industry practices and regulatory expectations for the aseptic processing of sterile drugs. It provides comparisons and outlines points of tension between curent manufacturing technology and capabilities with regulatory "requirements" for this important activity.

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In 1988, the Parenteral Drug Association (PDA) published a position paper on aseptic processing in response to intense interest in aseptic processing in the industry at that time and in partial response to the publication of the Food and Drug Administration's (FDA's) 1987 guideline on aseptic processing (1, 2). The intent of this review is similar to that of its 1988 predecessor: to identify and discuss the current capabilities of aseptic processing technology.

The improvements to aseptic processing operations described in the 1988 position paper were characterized in the opening section of that document as "evolutionary." The improvements in aseptic processing technology that have occurred since 1988 would perhaps be better characterized as "revolutionary." We believe that the practices described in 1988 are, by and large, as valid now as they were then. We also believe that products manufactured in compliance with the underlying principles outlined in the 1988 document are still inherently safe.

The aseptic manufacture of sterile products is perhaps the most difficult challenge faced within the healthcare industry. Aseptic processing requires the careful application of microbiological contamination control principles to exclude infectious organisms from sterile products. We reaffirm our belief stated in 1988 that, "the major variable in the control of aseptic processing arises not from the sterilization processes, the cleanroom, or the filtration processes that are so often the subject of technical papers and regulatory guidelines, but rather from the workforce itself" (1). Industry findings since 1988 confirm the earlier statement that human-borne contamination is the most critical risk factor in aseptic processing. Numerous industry surveys and technical articles published since that time are in accordance with this statement. (3–8).

Since the publication of the 1987 guidance, firms have continued to implement new technologies and aseptic processing improvements to better control human-borne contamination. At the same time, the industry has implemented expanded microbial-test regimens and more comprehensive process simulation testing to ensure that aseptic processing systems have adequate process capability and that this capability is consistent and as reproducible as possible within the technical constraints that are inherent in the measurement of aseptic performance.

This article describes the improvements in conventional and new technologies that have occurred since the late 1980s. It also describes the improvements that have been made in aseptic process validation and control. Finally, the paper discusses the technical limitations that still exist in the evaluation of aseptic processing and raises concerns regarding the increasing regulatory tendency to ignore the existence of those limitations.

The condition of asepsis

Since the earliest days of parenteral manufacturing it has been recognized that many drugs and biologics would not withstand a physical sterilization process in their final container. Currently, a majority of parenterals and other products labeled sterile are manufactured using aseptic processing (8). It is therefore appropriate to

Table I: Rank-ordered sources of microbial contamination in aseptic processing (3, 8).

	1986	2001
Personnel contaminants	1	1
Human error	2	2
Nonroutine activity	3	4
Aseptic assembly	4	3
Mechanical failure	5	5
Improper sanitization	6	7
Material transfers	6	8
Surface contaminants	7	7
Airborne contaminants	7	6
Routine APAactivity	7	7
Failure of 0.2 filter	8	8
Failure of HEPA	9	8
Improper sterilization	10	9
Other		10

review the concepts of asepsis and sterility before embarking on a discussion of key process requirements and validation principles for aseptic processing to clarify some of the misconceptions that have crept into industry and regulatory belief over the years. A vital element in process design and validation is a definition of the end-point. And it is not possible to establish an end-point and associated process control parameters without careful consideration of the target and the capability of the process.

We believe that industry and regulatory communities currently find themselves caught on the horns of a dilemma regarding aseptic processing. The dilemma arises directly from the seemingly logical but scientifically flawed notion that it is possible to prove that each and every lot of aseptically manufactured product contains only "sterile" material. *Sterile* is, if taken in its most absolute meaning, a word that offers no room for uncertainty in measurement or outcome. *Sterile* means free of any viable organisms (6). This condition, however, is not now and never has been possible to prove in aseptic processing.

This dilemma is not new—it has been recognized for decades and should never have left our collective understanding. What has changed since the publication of PDA's 1988 position paper is an understanding of the inherent limitations of any technology built around the exclusion of microorganisms rather than the physical destruction of those microorganisms. It seems to us that in the past most industry scientists and the regulatory community clearly understood that absolute sterility in aseptic processing was not possible and therefore did not reflect a reasonable expectation of outcome. It is now our belief that this appreciation is no longer as widespread as it once was.

In the past, the perspective of process capability for aseptic processing, and hence the requirements for process control, were more solidly grounded scientifically. As Block points out, there are pitfalls in using the word *sterile* in an absolute manner in practical applications (9). For example, we have long understood that process filters that produced safe product could not be demonstrated to yield sterile product in the "absolute" meaning of that word (10). In other words, we can always identify organisms that could penetrate any filter that is practical for use in aseptic processing. Absolutism is dangerous even in physical sterilization because it presumes that we can have discovered every existing form of microbial life.

When we use the word *sterile*—whether on a label or in a guidance document, standard, or regulation in the pharmaceutical industry—we must consider that the meaning of the word cannot be taken in a literal, absolute manner because doing so does nothing but ensure failure. While suggesting the acceptance of partial or incomplete sterility may be an anathema to those conditioned to think that parenteral manufacturing must be microbiologically perfect, it is our view that only by consideration of asepsis in a careful, scientific manner can we avoid unreasonable standards and correspondingly impractical regulatory enforcement. It is important to ensure that we as an industry are not trapped by semantics or impossible-to-achieve standards borne of misunderstanding.

Perhaps industry chose poorly by labeling aseptically manufactured products as "sterile." Little if any harm has come from this choice, however. In fact, it can be argued that the standards currently in place in industry clearly recognize the semantic tension between *sterile* and *aseptic*. No current standard calls for zero contamination in media-fill process simulation tests or in environmental monitoring, although several documents—including PDA's Technical Report No. 22—suggest that zero contamination is an appropriate target (6, 11, 12). We believe it essential to recognize the validity of zero as a target but at the same time remind industry and the regulatory community that this target may not be consistently and uniformly attainable because no aseptic environment or aseptically produced product is provably sterile.

The industry's approach to validation of aseptic manufacturing

In no other segment of the pharmaceutical industry is the control of manufacturing processes as critical as in the production of aseptically produced products. The recognition of the criticality of these processes has led to the continued development of advanced production and quality assurance systems. Firms have continued to develop and implement more rigorous methods for the validation of aseptic processes (13).

The resource and staffing requirements for validation programs within the industry have continued to increase during the past decade and a half. These increased validation efforts are comprehensive, including both prospective validation and ongoing validation maintenance. The management of a sound validation program requires the participation of specialists from various academic backgrounds in technical and administrative disciplines. Validation costs across the industry have certainly increased, and as might be expected the most costly of all operations to maintain in a validated state is aseptic manufacturing. Only part of the increased costs can be attributed to the increased technical complexity of aseptic operations. Substantial portions of the increased costs are a direct result of increased regulatory expectations. The following sections of this article present examples of the types of programs that make up the aseptic processing validation effort.

Sterilization validation and qualification of sterilizers. Comprehensive engineering qualifications are conducted on each new sterilizer to ensure that the design and functional specifications are met. These qualification activities are used as the basis for formalized change control programs that support the continued appropriateness of the sterilizer over time. In addi-

Table II: Media-fill survey comparison—acceptance criteria (19).

Criteria	1980		1986		1992		1996		2001	
<0.05%			3	11.5%	7	13.2%	4	7.5%	6	12.5%
0.05–0.09			2	7.7%	5	9.4%	12	22.6%	9	18.8%
0.10%	4	25.0%	19	73.1%	36	67.9%	51	92.6%	33	68.8%
0.11–0.20%	4	25.0%	1	3.8%	1	1.9%				
0.21–0.30%	3	18.8%	1	3.8%	5	9.4%				
>0.30%	5	31.2%								

tion, the maintenance procedures and calibration requirements for all process control devices are developed, as are the necessary standard operating procedures for these activities.

Following completion of the qualification of the sterilizer, process validation is undertaken to ensure that the sterilization process complies with regulatory requirements. These studies are designed to ensure that the conditions achieved throughout each sterilizer load result in the delivery of the appropriate lethality for the process. Equally important, manufacturing and quality assurance controls are designed to demonstrate that the sterilizer operates reliability and reproducibly under intended-use conditions during its operational life. Validation typically includes an adequate margin of safety to allow for process variation.

After the prospective validation has been completed, change control systems are established to ensure that sterilizers are maintained in a state of control. PDA commented in the 1988 position paper that "revalidation" studies that are essentially repeats of prospective validation studies on a periodic basis are not necessary. Unfortunately, PDA's position in this matter has not gained the broad acceptance it deserves.

In addition to periodic performance checks, calibration, and maintenance checks, firms enforce rigorous programs to ensure that no change is made to any aspect of the sterilization process or sterilization equipment without a full interdisciplinary evaluation. These change control programs are now far broader in scope and much more connected to the regulatory function within firms than they were in 1988. In the United States, firms follow regulations that define requirements reporting process changes to FDA. Similar practices are required outside the United States (12). Regulations defining reporting responsibilities for sterilization processes are far more clearly delineated than they were in 1988.

We are also concerned about the increasingly common practice of repeating validation studies on a more or less annual basis. There is no reason to believe that a sterilizer operating within validated parameters for physical operation should require periodic biological challenge testing. Modern steam and dry-heat sterilization equipment is robust and reliable. There is no scientifically valid reason to repeat biological challenges when the process control and engineering data indicate that the sterilization parameters and equipment function are consistently within target values. The imposition of unnecessary validation or revalidation requirements based upon unreasonable fear rather than scientifically meaningful analysis results in wasted resources and reduced productivity, with no benefit to end users.

Validation of sterilization procedures for components, containers, and closures that enter the aseptic processing areas. In 1988, PDA asserted that the sterility assurance level (SAL) of aseptically produced products was "generally considered to be 10^3 or more," while physical sterilization technologies used in component preparation resulted in an SAL of "at least 10^6." (It should be noted that PDA correctly presented the SAL value as a positive exponent, not to be confused with the probability of nonsterility concept use to assess risk associated physical sterilization methods, which is a fraction of one and therefore carries a negative exponent.) We believe that the sterilization of components is a very minor risk factor in aseptic processing, just as it was in 1988.

The predominant cause of contamination in aseptic processing remains the same as it was in 1988: activities performed by personnel in direct support of the aseptic process. Not only are personnel the major source of contamination, their actions serve to distribute the organisms within the environment. In PDA surveys on aseptic processing conducted in 1986 and again in 2001, industry opinions regarding the sources of contamination in aseptic processing were virtually unchanged (see Table I). Table I also shows that the seven most prevalent sources of contamination—identified as most likely to contribute microbial contamination during an aseptic process—all are related to activities performed by operators and are virtually unchanged in relevance during the 15 years between these surveys.

We also have seen shifts in the technologies applied for the sterilization of components. Since 1988, environmental and occupational safety concerns have greatly reduced the utilization of ethylene oxide (EtO) for the sterilization of plastics and other non–heat stable components. Of course, EtO is still used and is still an extremely efficacious gas sterilant.

However, several other technologies with similar levels of sterilization efficacy have been introduced or have expanded in their use. Both gamma and beta (electron beam) sterilization were used in 1988, but they are more widely used today. Lower-energy radiation technologies are coming into increasing use in sterilization of heat-labile materials. Also, new gas- or vapor-sterilization methods have been introduced. These include vapor phase hydrogen peroxide and chlorine dioxide.

In some respects, the methods used for component sterilization in the manufacture of glass and elastomeric stopper container systems have changed little since 1988. Moist-heat sterilization continues to be the most widely used sterilization method, and validation technology and efficacy have changed little since 1988. Validated moist-heat sterilization processes continue to result in an extremely safe outcome.

Dry-heat depyrogenation continues to be the method of choice for the sterilization and depyrogenation of glassware. Industry develops and validates depyrogenation processes to yield at least a three-log reduction of reference-standard bacterial endotoxin. The resistance of endotoxin to heat is at least an order of magnitude greater than even the most resistant spore, therefore a three-log or more reduction

in endotoxin results in a very low probability of nonsterility, far lower in fact that 10^{-6} (SAL $> 10^6$).

The most significant process risks associated with component handling have always been the aseptic handling required in the initial setup of component supply systems such as parts hoppers and feed chutes poststerilization and in keeping aseptic processing operations supplied during manufacturing. In 1988, supplying components was largely a manual process. The widespread adoption of continuous washing and depyrogenation of glassware using "tunnel" systems began in the late 1970s and was well underway in 1988. At that time, many aseptic filling operations required operators to supply the filling line with depyrogenated glass. Today, continuous glassware washing and depyrogenation without the need for human intervention to supply the filling machine is standard practice in all but the lowest throughput operations. The incremental improvements in operational efficiency of the continuous glassware-processing systems have led to higher levels of throughput, while human interventions for maintenance, correction of jams, or removal of fallen containers have been reduced or in some cases essentially eliminated.

Similarly, a great deal of engineering effort has been invested in developing stopper processing systems that minimize human intervention. Continuous stopper processors with continuous automated supply have been introduced. Also, in batch component feed operations, advanced aseptic technologies such as restricted accesses barriers (RABS) or isolators equipped with rapid transfer port (RTP) technologies have all but eliminated the risk of human-borne contamination.

Of course, many aseptic processing operations continue to rely on human operators to supply components using aseptic techniques. Some significant improvements have been made in cleanroom clothing during the past decade and a half. These improvements have led to safer human-scale cleanroom operations. The filtration properties of cleanroom clothing have improved, for example, and new hood, goggle, and face-mask systems have resulted in less skin exposure, better sealing, and improved operator comfort.

The 1988 PDA paper clearly stated "The threat of contamination in aseptic processing arises not from the sterilization processes, the cleanroom, or the filtration processes which are so often the subject of technical papers and regulatory guidelines, but rather from the workforce itself" (1). As a consequence, equipment suppliers, cleanroom suppliers, and the pharmaceutical industry itself have reacted to this challenge, systematically reducing the risk of contamination. The continued implementation of automation and advanced aseptic processing technologies will continue to incrementally reduce risks associated with human-borne contamination in aseptic processing.

Process filter validation. The basic principles involved in product filtration are generally the same today as they were in 1988 (15). Firms continue to carefully as-

sess fluid bioburden and use these data to reaffirm the appropriateness of their filtration systems. Firms generally reassess bioburden on a periodic basis and clearly define hold times and the temperatures of materials that reduce the opportunity for microbial survival. The highly specialized nature of filter validation generally requires considerable participation by filter vendors.

Of course, there have been improvements made in filter technology and in its process control since 1988, including

- improved materials of construction of filter cartridges that have allowed for greater use of *in situ* sterilization
- using preassembled cartridge filters rather than manually assembled filter disk sets throughout the industry, thereby reducing the opportunity for errors in assembly
- improved vent and gas filters with greater strength and reliability
- increased usage of reliable sterilize-in-place technology on both vent and process filters, which further reduce aseptic connections and manipulations
- improved automated systems for *in situ* evaluation of filter integrity.

Process simulation testing. It is our belief that PDA's 1996 technical report that focused on the validation of aseptic processing is still the most comprehensive treatise on process simulation or media-fill testing of aseptically manufactured products (6). The reader is referred to that document for detailed guidance regarding the design of media-fill tests and the interpretation of results.

Much of what was described as standard industry practice in the 1988 position paper is still suitable today. Evolving regulatory doctrine for media-fill test requirements has become increasingly burdensome. Unfortunately, however, this has not increased end-user safety. Particular concerns include media-fill container rejection issues, length of fill and number of units filled, personnel qualification, and revalidation practices (16).

During the past few years, FDA has applied considerable pressure regarding the rejection of units from the media-fill population that is incubated and inspected. FDA's concern in this regard is understandable: The media fill should not be biased by the removal of containers a firm believes might have been compromised, therefore yielding an unwelcome result. The media-fill test must always be a scientifically valid evaluation of the aseptic process, and, as such, there can be no room for artificial biasing of the outcome toward success.

On the other hand, it is unreasonable for regulators to hold that all media-filled units—particularly those that would be rejected because they lack container/closure integrity—should be incubated even as a separate population. Incubation of containers that normally would be rejected for lack of container/closure integrity accomplishes nothing. We agree that units should not be rejected from the media-fill test population for cosmetic defects only, even if they would normally be rejected in prod-

uct manufacturing.

It is our opinion that far too much has been made of this issue. It is possible to ascertain whether a media fill is representative in terms of rejects by simply comparing the normal lot rejection rate for container/closure integrity with that of the media-fill test. It is clear that the reject rate should not be higher in media fills than in normal production runs of comparable size. On the other hand, it is equally clear that they should not be expected to be consistently lower either. The alignment of intervention practices for production and media fills should ensure this consistency of performance.

In 1988 the number of units incubated by most firms in a media-fill test was almost always 3000 or slightly more. The number of media-filled units since 1988 have increased since the introduction of higher throughput aseptic processing filling systems. In operations with fill speeds at least 200 units/min, the duration of a media fill in which the target population was only 3000 would result in a media fill that might last substantially less than 30 min—not including set up. However, requiring media-fill tests that are a high percentage of the total number of units filled in a batch is not necessary to assess process capability. Media-fill populations of more than 10,000 units are rarely, if ever, required even for high-throughput operations.

Companies also conduct longer duration fills to test operator fatigue. During the past 25 years, industry has conducted media-fill tests under a wide variety of conditions, including so called "piggy-back" media fills done at the end of a normal production fill. There is no evidence indicating that operator fatigue is a factor in environmental control, media-fill outcome, or product safety (17). Nevertheless, there is no need to fill enormous quantities of media for this sole purpose of evaluating fatigue because the more automated an aseptic operation is the less likely fatigue will be an issue in asepsis. Each firm should perform risk analysis to ensure that their media-fill tests are representative evaluations of their processes, adjusting media-fill sample size accordingly.

There should be no fixed requirement for each operator to participate in a media-fill test before being admitted to aseptic production work. Abundant means exist to qualify personnel for aseptic operations without the requirement for at least one media-fill test. Each employee can be evaluated in terms of gowning effectiveness, and laboratory simulations can be used to evaluate their aseptic technique (6, 8). In addition, operators can be comprehensively trained on equipment operations and relevant operating procedures and work instructions. Critical personnel, including those required to perform equipment set-up and critical aseptic assembly, should be required to successfully participate in a media-fill test before taking up their work assignment.

There is no need to conduct more than one media-fill test per operational shift per year. More-frequent media fills on validated production lines are unnecessary.

It is also unnecessary to test each container type each year. A firm should develop a rationale for their container/closure system selection on the basis of a careful analysis of risk (6).

Media-fill tests are quite useful, but they are not without limitations. Media-fill results can lead a firm (or a regulatory inspector) to conclude that an operation is much better or much worse than it actually is. It is important to remember that a media-fill test is a snapshot in time and is not always predictive of future outcome or informative regarding previously manufactured product. Certainly a zero contamination target is appropriate and media-fill positives should occur rather rarely. However, this does not mean that a single contaminated unit should be the cause of product quarantine or rejection. Modern aseptic cleanrooms are outstanding, but they are not perfect. The quarantine or disposal of safe product because of unwarranted concerns about "sterility assurance" is wasteful and not scientifically supportable. Documented improvements in aseptic processing performance are somewhat difficult to support in a quantifiable manner. One measure of industry performance is the increasingly tighter limits placed on media fills since 1980 (see Table II).

That firms are voluntarily reducing their acceptance criteria for media-fill contamination rates below 0.1% supports the continued improvements that have been made to aseptic processing. A comparable assessment can be found in *USP,* where a recommendation has been made that two out of three media fills should be devoid of contamination (20). Coupled with the near absence of documented evidence indicating the presence of actual microbial contamination in sterile products, this suggests that sterile products manufactured by aseptic processing are safer than ever.

Environmental systems and controls

Essential elements of the environmental control and facility management program. The basic elements of an aseptic processing environmental control program have not changed since 1988 and still consist of

- a review of environmental factors that generally include temperature, relative humidity, air velocity, unidirectional air flow, HEPA filtration, and pressure differentials between rooms of different classification
- an evaluation of utility services that could affect microbiological safety or product quality
- a comprehensive microbiological and total-particulate monitoring system
- an evaluation of personnel gowning and materials transfer airlocks
- calibration, certification and preventive maintenance on critical facility systems and processing equipment
- training programs for personnel in both aseptic technique and standard operating procedures or work instructions.

These systems should be subject to regularly scheduled and unscheduled audits and routine supervisory oversight and evaluation.

Cleanroom classification. The classification of each room or module within an aseptic processing area must be appropriate for its intended use. The highest level of control will be directed to those areas, typically known as critical zones, in which aseptic manipulation of uncovered containers, closures, or components occurs. These areas are designed to comply with Class 5 of ISO 14644 (ISO Class 5 is functionally equivalent to traditional US Federal Standard (FS) 209 E Class 100, and to EU Grade A)(12, 21, 22). These areas are equipped with total-coverage HEPA filtration, and unidirectional airflow is maintained to the extent it is technically possible to do so.

European and United States aseptic processing area zoning differs: In the United States, the area immediately adjacent to the critical zone is typically Class 7 (FS 209 Class 10,000). In Europe, this area is Grade B, for which there is no precise analog in either the ISO or now withdrawn (replaced by ISO 14644) FS 209E classification schemes. These classification schemes, however, can be considered functionally equivalent provided validation testing and ongoing environmental controls indicate that performance is in compliance with existing guidelines and standards. Firms may use different approaches provided they have a rationale based upon good scientific and engineering practice. It may be beneficial to include a HACCP analysis to support a firm's cleanroom design strategy for an aseptic operation.

Other parameters typically considered in the design of an aseptic processing area are direction of airflow, air balance, air changes per hour, and air velocity. There are numerous engineering guidelines containing sound design recommendations for aseptic processing areas (23). These recommendations have changed very little since 1988, essentially because the design features known to be important in 1988 are still recognized as vital to good cleanroom design today.

There has been a tendency for both air velocity and uniformity of airflow to be overemphasized in today's regulatory environment. The 90-ft/min or 0.45 m/s air velocity requirement is a reasonable and effective target value. However, it is not reasonable to conclude that these values are in any way sacrosanct (24). In fact, before the publication of the 1998 position paper, all references to air velocity were removed in FS 209C and do not appear in ISO 14644-1, which replaced FS209E. The adequacy of an air velocity and the closely related specification of air changes per hour depends upon several factors, including total room volume and location of the HEPA filter or air entry point relative to the work zone. Therefore, quite different velocities may provide similar levels of performance depending upon the design and usage of the facility.

One must also recognize that when air velocity was included as a cleanroom design specification, measurement of air velocity was taken approximately one foot from the face of the HEPA filter. There is no basis to require that any specific air velocity be attained at the work surface. The work surface, because it is oriented essen-

tially perpendicular to the direction of air supply, will interfere with the airflow and make the reproducible measurement of air velocity at that level problematic. This is a reality of aseptic processing critical zones that existed in 1988 and will continue to exist in the foreseeable future.

Because the work surface is located perpendicular to the direction of airflow and because the work surface cannot be made aerodynamic, maintenance of strict unidirectional airflow at the work surface is not possible and cannot be reasonably expected. Visualization of airflow may be beneficial for optimizing air movements; however, more meaningful evaluative information can be obtained using the Ljungqvist-Reinmüller method (25).

Visualization (commonly called "smoke studies") is subjective because human observers commonly judge the outcome without any clearly delineated criteria. Differences of opinion regarding what constitutes good or bad airflow are thus commonplace. Visualization has been overemphasized by regulators and should not take precedence over objective data indicating that there are reliable aseptic conditions regardless of the observed flow patterns.

Another measurement that has been overemphasized during the past decade has been the uniformity of airflow from HEPA filter to HEPA filter as well as across the face of a HEPA filter. Expectations regarding airflow should be realistic and must consider the variable performance characteristics of HEPA filters as well as the accuracy of the velocity measurement. The current frequency for HEPA filter recertification in the industry is 6–12 months and has proven quite adequate. Monitoring differential pressures across the HEPA filters is enough to ensure that the filters are performing properly between recertification events.

In 1988, PDA noted that cleanroom design and operation guidelines should not be applied too rigidly. This situation has not changed. No cleanroom design, operation standard, or guideline is comprehensive and most contain information based upon collective industrial experience rather than unequivocal scientific or engineering facts. A suitable process is best defined by its validated ability to manufacture product having the required quality attributes. Evaluating processes requires thoughtful analysis by experienced, well-trained technicians.

Environmental monitoring. Comprehensive environmental-monitoring programs were a general practice in the industry in the late 1980s. Since then, these programs have become even more expansive (26). Unfortunately, there is no evidence that the environmental programs of today are functionally superior to those of 15 years ago. They are certainly more costly and far more time-consuming, but we do not believe that they do a better job of assessing product safety.

The basic sampling methods and approaches to environmental monitoring have changed very little. What has changed is the amount of monitoring conducted and the actions expected by regulatory inspectors in the event of excursions. Envi-

ronmental excursions, results that exceed action levels, occur at a slightly lower frequency than they have in the past. This is due to improved equipment design that has reduced cleanroom population, better air movement, and probably most significantly improved cleanroom clothing.

We believe that the industry, in part through regulatory pressure, is now misusing environmental monitoring to a significant degree. The inherent uncertainty and inaccuracy of environmental monitoring are increasingly forgotten, and in far too many instances the results of sampling are considered something of a product release microbiological quality assay (24). In the most extreme cases, namely samples required on so-called "critical surfaces," environmental monitoring has all too often evolved into a *de facto* product-release sterility test. This is scientifically inappropriate. We object to the application of Barr decision-like out-of-specification (OOS) test interpretation and resolution in the event of environmental monitoring excursions. FDA's OOS guidance was never intended for application to microbial testing, and this position has been reaffirmed numerous times by the appropriate FDA personnel (27).

Environmental monitoring must take into account the realities of microbiological growth and recovery. The measurement accuracy of active air samples, often but erroneously called "quantitative" air samplers, is limited. A study by Reinmüller and Ljungqvist found that the variability among commonly used active air samplers can exceed five-fold (25). Clearly then, setting an action level of 3 colony forming units (cfu) and an alert level of 1 cfu is not logical. In addition, microbiological enumeration, particularly at low organism titers, is prone to significant variability. Therefore, it is more scientifically reasonable to monitor trends by evaluating contamination incidence rates rather than by placing stock in counts of colonies.

The environmental sampling plan should include representative sites in the ISO Class 5 critical zone as well as the surrounding environment. These sites should be sampled daily. Noncritical surfaces such as walls and floors should be sampled weekly to ensure that the firm's disinfection program is performing adequately. Routine environmental sampling on personnel should be limited to glove testing, although more-intensive personnel sampling on a quarterly basis may be desirable in some cases.

Direct sampling of product-contact surfaces such as parts hoppers or bowls and filling needles may be conducted, but the results should not be considered indicative of sterility or asepsis. Many firms consider sampling on these surfaces unnecessary and we don't consider data collected on these sample sites as any more important than air sampling. In fact, recent studies conducted by PDA demonstrate that surface contamination is a poor predictor of media-fill outcome (28).

It may seem logical to believe that anything less than perfect environmental results indicate a loss of sterility assurance. However, this opinion is not scientifically

valid or supportable. It is unreasonable to expect an aseptic environment containing human operators to be sterile. Industry has long understood that the word *sterile* must be defined in a less than absolute manner if it is to be used at all in the context of aseptic processing. Using environmental monitoring as a product-release test is inappropriate because sampling can neither prove nor disprove that contamination exists in any given unit or lot. Monitoring is today exactly what is was 15 years ago: a method for assessing that the process control asserted in a cleanroom is within compliance with general industry standards and that it is maintained within process capability. The meaning of single-point excursions is unclear and should not be overinterpreted.

Most important though, we must, as an industry, focus on product safety rather than on an absolute and abstract expectation that a perfect sterile environment must exist. Sterile rooms do not exist, and they never have. Rejection of product owing to environmental excursions even on critical surfaces is a game of chance, rather than a valid quality control procedure. The current regulatory-driven approach to environmental monitoring is one area in which aseptic processing has not improved since 1988.

Advanced aseptic processing. *Advanced aseptic processing* can be defined as technologies that through automation or environmental separation actively or passively reduce risk from human-borne contamination. Because human-borne contamination is really the only risk of consequence in human-scale cleanroom aseptic processing, it should be obvious that technologies that reduce the likelihood of operators releasing microorganisms near open product or components can further improve the already impressive safety achieved in aseptic processing.

Advanced aseptic technologies include isolators, restricted access barrier systems (RABS), blow– or form–fill–seal technologies, and various types of machine automation. The upsurge in the implementation of these technologies is visible throughout the industry (8). In 1988, the first isolator-based aseptic filling systems were just being implemented, today these systems number in the hundreds. Blow– or form–fill–seal technologies have been used in industry for more than 30 years and continue to undergo incremental improvement. RABS systems provide a means of upgrading existing aseptic processing systems by reducing the likelihood of human-borne contamination in critical operations. Examples of reduced risk through automation abound and include loading of lyophilizers, component replenishment, and checking and adjustment of container fill weight.

In 1988, PDA cautioned that, "A dogmatic approach could stifle the development and implementation of technology which could markedly improve the SAL of sterile products" (1). Unfortunately, neither industry nor the regulatory community heeded PDA's advice (29). In the case of isolator technology, bad decisions made by industry advocates and regulators have hampered implementation, particularly

in the United States.

Industry advocate groups made the mistake of setting a target of performance for isolators equivalent to terminal sterilization. This was a very unfortunate strategy because the demonstration of equivalence in terms of absolute sterility is impossible. This mistaken target setting resulted in a plethora of validation expectations that were difficult to understand and implement. Targeting perfection resulted in the expectation of a perfectly sterile enclosure environment, perfect transfer technologies, and perfect system integrity. In the case of leaks, the actual microbiological significance of so-called "breaches" wasn't considered and instead theoretical notions of perfection replaced a pragmatic approach to systematic technological improvement.

We believe that advanced aseptic systems have more than met the expectations we had for them in 1988. Industry and regulatory authorities need to see these technologies for what they are: an important incremental improvement in asepsis arising from reduced human-borne contamination risk. The target for validation of these systems should be improvement over conventional cleanrooms, not equivalence to terminal sterilization. It is illogical and therefore inappropriate for firms to concern themselves with abstract or theoretical risks that cannot be measured (30).

Validation techniques for these systems should not be appreciably different than those used for conventional cleanrooms, although their process capability is higher. Obviously this higher capability should be reflected in the in-process control and validation acceptance criteria used for these more technologically advanced systems. However, we reiterate that perfection is not currently attainable and that we lack the tools necessary to measure perfection. It is wrong to allow perfection to be the enemy of good.

Summary

We believe that aseptic processing in our industry has improved markedly since 1988, including

- improved cleanroom garments and a better understand of modes of contamination
- improved cleanroom designs and op-

erational performance
- more comprehensive employee training and qualification programs.
- improved aseptic processing equipment requiring fewer line interventions
- well-established validation programs incorporating sound change-control practices to ensure continuing reliability of the processes
- implementation of advanced contamination control technologies such as isolators, restricted access barrier systems (RABS), and blow–fill–seal or form–fill–seal systems.

The industry as a whole has earned an enviable safety record in aseptic processing over the years. In 1988, aseptic technologies operating in compliance with industry and regulatory guidelines resulted in product that was unquestionably and unequivocally safe with respect to microbial contamination. Today, as in 1988, the weakest link in the sterile and aseptic product delivery pathway is at the level of administration rather than manufacturing. Logically, those concerned with patient safety would seem better advised to focus their energies where they are likely to have the greatest effect.

There have, of course, been recent reports of firms releasing aseptically processed products that purportedly lack sterility assurance. We do not doubt that in very rare instances product has been made in a manner contrary to good contamination control practice. However, it is inappropriate to punish the many for the sins of a very few. Those firms lacking the commitment to manufacture "sterile" products in an appropriate manner should have known better. Successful production of "sterile" products using aseptic processing can certainly be made possible if the precepts outlined within this article are ascribed to.

Perfection in aseptic processing is not currently achievable, because an absolute demonstration of unequivocal sterility assurance is not possible. However, safety is both possible and routinely attained, and for that industry can be proud. Industry understands that continuous process improvement in our performance, especially in the production of "sterile" products is not just desirable, but essential. We have no doubt that in the coming decades risks from microbial contamination will be even better controlled than they are today. After all, the only significant source of contamination is widely recognized, and there are superb methods for minimizing this risk even further than is possible today.

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