

Aseptic Processing: A Vision of the Future

James Agalloco* and James E. Akers

ADVANSTAR
COMMUNICATIONS



DSM PHARMACEUTICALS

Continued technological improvement, beyond what is commonplace today, is the only real way to achieve continued improvement in aseptic processing.

James Agalloco is the president of Agalloco & Associates, PO Box 899, Belle Mead, NJ 08502, tel. 908.874.558, jagalloco@aol.com. He is also a member of *Pharmaceutical Technology's* Editorial Advisory Board. James E. Akers, PhD, is the president of Akers Kennedy & Associates, 1215 W. 60th Terrace, PO Box 22562, Kansas City, MO 64113-0562, tel. 816.822.7444, akainck@aol.com

*To whom all correspondence should be addressed.

Aseptic processing is the method used for producing sterile products if terminal sterilization would adversely affect the product. Because terminal sterilization processes kill microorganisms, they are more certain to prevent product contamination than aseptic processing methods, which aim to exclude microorganisms from the operating environment. Even if the active pharmaceutical ingredient is compatible with terminal sterilization, however, aseptic processing sometimes is the preferred processing choice. For example, a drug delivery system that is incompatible with terminal sterilization may be a good choice because it reduces the risk of contamination when the product is administered to a patient.

Microbial contamination in aseptic processing is mainly caused by personnel. It is estimated that more than 99% of all microorganisms detected in cleanrooms are of human origin. The passage of microbes through the HEPA filters supplying air to the cleanroom is highly unlikely given the filter's effectiveness for particle retention (typically $\geq 99.997\%$ for particles $> 0.3 \mu\text{m}$). Other items present in the cleanroom—such as product on equipment—might generate nonviable particles during operation but cannot be considered significant sources of viable contamination.

The principal challenge in aseptic processing is to maintain a consistently high level of microbial control over the environment. In staffed environments, this is a substantial challenge because personnel, even those who use good aseptic techniques while working and remain largely inactive between interventions, continuously shed microorganisms at relatively high rates (perhaps $> 10^6$ organisms per hour), and the gowning materials and clothing used must be relied on to exclude these organisms from the sterile items being processed. Proper operation and management of aseptic environments to minimize microbial contamination are difficult, demanding, and exacting tasks. The following are commonly observed shortcomings:

- Over-reliance on manual assembly and human manipulations in aseptic cleanrooms rather than relying on equipment automation and closed systems during the aseptic process;
- Gowning materials and systems are not fully effective (e.g., not hermetically sealed), and the environment and methods for gowning are similarly deficient;

- Because of a general lack of automation, process equipment setup and operation require personnel interventions for nearly all activities;
- Insufficient and improperly optimized air movement, e.g., too few air changes (a problem often seen in facilities built in the 1980s or earlier);
- A paucity of processing systems capable of black or even gray side equipment maintenance and adjustment;
- Poorly conceived materials entry and component feeding systems, e.g., parts hoppers and feed systems that cannot be decontaminated *in situ* or sterilized;
- Manual steps are retained for operations that can be automated easily (e.g., weight checking and weight adjustment);
- Equipment and components are of inadequate quality and require frequent human activity to correct jams, stoppages, and other operating errors.

Personnel: the primary source of microbial contamination

Firms sometimes appear to operate on the premise that interventions do not matter and that almost any intervention can be justified by including it in media fill tests. But the best control of microbial risk is attained by considering how to eliminate interventions rather than by ensuring that all interventions are covered during a process simulation test. Substantial emphasis is placed on gowning materials and operator gowning qualification; perhaps this leads to a false sense of security regarding the level of asepsis that can be attained by gowned personnel. The proper attitude recognizes that successful gowning and passing results on gown qualification monitoring tests, although important, do not ensure a safe aseptic environment.

For optimal control of contamination risk in aseptic processing, it must be acknowledged that interventions by the operator in the critical environment always increase the risk of microbial contamination in a sterile product. It must be recognized that the best intervention is one that never occurs because the process and equipment were designed to eliminate it. Eliminating human interventions should be a universal goal for aseptic processing, especially in staffed cleanrooms. Sadly, this is not the case, and interventions in aseptic processing are considered normal and acceptable.

Because the release of microbial contamination by gowned personnel is inevitable, the recovery of microorganisms within the cleanroom should be considered normal. Sterility even aseptis cannot be expected or proved in even the most modern staffed aseptic facility. This is true even if we define *sterility* as merely the absence of recoverable viable organisms, which is a very liberal definition. Activities that result in microbial contamination in cleanrooms have been considered in various PDA surveys on aseptic processing practice (see Table I) (1, 2). The top factors associated with contamination in staffed cleanrooms have been personnel or the activities that they perform (personnel are involved in all of the top 6–7 causes).

Examining the effect of personnel on the aseptic processing environment highlights the need for attention to them. Table II lists the activities and systems that make up the aseptic process. It should be apparent that those that involve the participation of personnel are less well-controlled and also are more likely to

Table I: Top contamination sources in cleanrooms in 1986 and 2001.*

	1986		2001	
	Rank	Raw data	Rank	Raw data
Personnel contaminants	1	1.78	1	2.00
Human error	2	3.04	2	2.55
Nonroutine activity	3	4.20	4	4.95
Aseptic assembly	4	4.47	3	4.75
Mechanical failure	5	5.23	5	5.65
Improper sanitization	6	5.80	7	6.82
Material transfers	6	5.81	8	7.46
Surface contaminants	7	5.93	7	7.02
Airborne contaminants	7	5.96	6	6.73
Routine activity in aseptic process area (APA)	7	5.98	7	6.95
Failure of 0.2- μ m filter	8	7.42	8	7.30
Failure of HEPA filter	9	7.90	8	7.58
Improper sterilization	10	8.11	9	7.76
Other			10	8.33

*Adapted from references 1 and 2.

Table II: The effect of personnel on the aseptic processing environment.

Task	Ease of validation	Sensitivity to personnel	Associated risk
Sterilization	Easy	Low	Low
Room design	n/a	n/a	Moderate
Monitoring	Moderate	Variable	High
Sanitization	Difficult	High	High
Gowning	Difficult	Very high	Very high
Material transfer	Difficult	High	High
Aseptic technique	Difficult	Very high	Very high
Aseptic assembly	Difficult	Very high	Very high

result in contamination to the environment and potentially to the product as well.

This view is shared by regulators. Hank Avallone, who trained a legion of FDA investigators, used to remind his audiences continually that, "It is useful to assume that the operator is always contaminated while operating in the aseptic area. If the procedures are viewed from this perspective, those practices which are exposing the product to contamination are more easily identified." (3) If proper attention had been given to this sage advice, perhaps the cleanrooms of today would be more capable of making our processes safer. This view persists within FDA, as evidenced by the following passage from the agency's latest guidance on aseptic processing, which states, "A well-designed aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases" (4).

The importance of personnel in aseptic processing has certainly been acknowledged, and the industry pays considerable

attention to operators' competencies. All manner of activities—training programs, gowning certifications supervisory evaluations, personnel monitoring, and the ultimate process simulation—are carried out to establish that operators are proficient in aseptic operations. Regrettably, none of these can truly support operators' capabilities at all times. The most reliable means of assessing aseptic performance is frequent observation by supervisors and in-depth coaching. In today's industry environment, however, often little time is available for quality management or production supervision, including observation and coaching.

In addition, an operator's ability to perform a particular task successfully, even if demonstrated multiple times, does not ensure that the operator will perform that same task perfectly on every occasion. Success in a media fill test or even several media fill tests cannot ensure that a continuously high level of performance will be attained. We must acknowledge that human performance is variable and thus that we are at risk for microbial contamination every time an operator performs any activity in a cleanroom.

Regulatory perspectives on microbial contamination in aseptic processing

FDA has endeavored to impress upon the industry the criticality of human activity in cleanrooms. The latest guidance includes statements such as the following:

"No microorganisms shall be detected in Class 100."

"Product contact surfaces must be sterile."

"Media fills shall have no contamination." (4)

These stated aseptic processing objectives mandate perfection at all times. That these conditions are considered normal performance by FDA highlights the criticality the agency places on the aseptic process and how closely our attention must be on the operator activity required by the aseptic process.

Industry response. Rather than address the problem head-on, by eliminating interventions entirely, industry's approach has been to change the manner in which interventions are performed. Innovative technologies (e.g., barriers, isolators, blow-fill-seal systems) have been introduced in an effort to eliminate person-borne contamination from the critical environment by either altering the interventions, or changing how they are performed. Isolators, which are currently the pinnacle of aseptic processing technology, still do not eliminate manual interventions. Glove failure in an isolator risks human-derived contamination in critical locations. Many of the other technologies mentioned have similar or other weaknesses that make them less capable than the isolator.

Isolators: the "state of the art"

The transition away from staffed cleanrooms and toward isolators is a significant step in the right direction because isolators remove personnel from critical aseptic process environments. Isolation technology represents the furthest industry has gone toward mitigating the risk of contamination of human origin.

Not everything associated with isolator implementation has been positive, however. Isolator integrity, for example, has proved

to be a more nettlesome problem than anyone anticipated. And the application of isolation technology requires great care in process design and equipment selection. Access to the inside of the isolator is severely restricted by gloves (or half-suits), so ergonomics takes on added significance. Isolators still rely heavily on the use of gloves (and thus, on human activity) to conduct many required activities. In fact, the most-used gloves are often the most essential for the aseptic process; those used for equipment setup, routine and nonroutine interventions, and environmental monitoring.

In addition, despite the accepted advantages of isolator technology in aseptic processing capability relative to staffed cleanrooms, the acceptance of isolator technology has been slow, particularly in the United States, because of perceptions of long and troublesome validation processes and rigorous regulatory expectations. Decontaminating isolators has turned into a regulatory compliance debating point, in which the scientific principles are often poorly understood by the participants in this debate. The improvements in aseptic processing resulting from using isolators has been about what should have reasonably been expected. However, expectations have been unfulfilled because of unreasonable regulatory pressure resulting from a desire to achieve levels of performance on par with terminal sterilization.

Perhaps an even more important cause for the failure of isolators to meet expectations are mediocre design, engineering, and execution. The key feature of isolators intended for aseptic processing is their ability to exclude microbial contamination. Although isolators certainly are superior in this regard to a staffed cleanroom, isolators aren't perfect. Despite any decontamination treatment they are given, they cannot be considered sterile; sterility or even asepsis cannot and never will be proven. The potential ingress of contamination from gloves remains an unavoidable risk. The recovery of organisms in the isolator is substantially reduced relative to cleanrooms but is still not absolute.

FDA and isolators. FDA has weighed in on isolation technology in relation to aseptic processing, stating, "A well-designed positive pressure isolator, supported by adequate procedures for its maintenance, monitoring, and control, offers tangible advantages over classical aseptic processing including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems" (4). The focus of much of FDA's concern relative to isolators is gloves and glove integrity, as observed in various agency statements:

- "A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity."
- "An attentive preventive maintenance program can identify and eliminate gloves lacking integrity and will minimize the possibility of placing a sterile product at risk. Such a breach can be of serious consequence."
- "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."

Because the gloves on the isolator are used for all activities, the risk of glove-derived contamination is less than that of a gowned individual in a cleanroom; nevertheless the gloves are perhaps the weakest element in the isolator system. The primary risk with isolators that use gloves is essentially identical to that of the staffed cleanroom: microbial contamination derived from personnel. The benefit of isolators is that the magnitude of the risk is reduced.

Thus, success in aseptic processing, regardless of the technology used, depends upon the proper execution of critical manipulations of sterilized materials in an extremely clean environment using systems to minimize microorganism transfer. The focus of attention must be on personnel because they are the only significant source of microbial contamination.

Recognizing that personnel are the contamination source of concern has led to designs that exclude them. The design approaches usually rely on methods that:

separate personnel from the environment:

- flexible barrier systems,
- rigid barrier systems,
- restricted access barrier systems, or RABS);

limit their interaction with sterile materials:

- blow-fill-seal,
- form-fill-seal,
- robotics,
- advanced machine designs;

entirely remove personnel from the environment:

- closed isolators,
- open isolators;

Some combination of the above:

- form-fill-seal in an isolator,
- robotic manipulation inside a barrier design).

The ultimate goal of aseptic processing is to completely eliminate microbial contamination, thereby eliminating risk to the patient. Reducing personnel-borne contamination by using isolators is a reasonable first step. Fully eliminating microbial contamination might be possible in an isolator equipped with robotics or automation that eliminates the use of gloves.

Aseptic technology in the future

The next logical step for aseptic processing is completely eliminating human-borne contamination, which can only occur by completely eliminating human intervention. That would require removing personnel from every aspect of the process, including the key activities of:

- setup and assembly of the aseptic processing equipment
- routine and nonroutine (corrective) interventions
- environmental monitoring
- system changeover.

An emerging regulatory trend is to consider risk levels in the review of pharmaceutical activities. In a risk-based approach, regulators' focus is on products, operations, and activities that present the greatest risk to the patient. Proper consideration of risk will enhance patient safety while conserving resources. All sterile products will, of course, be considered "high risk" because difficulties with these products can result in the most serious consequences for patients. And among sterile products, those

produced by aseptic processing present the highest risk concern and as a result will undoubtedly remain the most scrutinized.

The use of aseptic processing technologies incorporated risk management well before *risk management* became a regulatory buzzword. Barrier designs, blow-fill-seal systems, and isolators all have been used for manufacturing and filling aseptic products for more than 20 years, so nothing about risk mitigation in relation to aseptic processing is new. The questions to be asked are: Should we do better? Can we do better?

The answer to the first question must be an emphatic *yes*. Most patients receiving sterile drug products are already ill and may have a weakened ability to resist infection. Ideally, therefore, aseptically produced drugs should result in no risk to the end user. With this goal in mind, aseptic processing capability has improved steadily during the past 20 years, in no small part to advances in technology. Although the actual levels attained cannot be reliably determined, our best estimate comes from the results of media fills, and a 2003 survey found that ~90% of all media fills had no contamination (5). But tolerating processes with a capability no better than 1 nonsterile unit in 10,000, 100,000 or even 1,000,000 units is simply not good enough. This is made clear by the words of John Sharp, a distinguished expert in current good manufacturing practices, who said, "It's okay as long as you aren't the millionth bloke!" (6). Continual efforts must be made to improve aseptic processing performance beyond current capabilities. A key driver in this will be regulators, who are properly fixated on aseptic processing and have raised their expectations numerous times during the past 30 years. Media fill acceptance criteria have tightened from 0.3% of filled units in the late 1960s, to 0.1% in the 1980s, to current criteria of 0.01% (4, 7, 8)

Advances in aseptic filling technology

If we acknowledge that we should continue to improve performance, then we must address the second question: Is further mitigation of risk from human contamination possible beyond the capabilities of current technologies? Today's aseptic processing systems clearly are more capable than those of the past. Industry surveys in which the performance of various aseptic processing technologies has been assessed clearly support that the aseptic processing innovation has provided superior results (1, 2, 9). These designs may have contamination levels approaching 1 in 100,000 or better. Although these systems are certainly superior to the staffed cleanroom that is still in common use, they are not perfect and never will be. Progress beyond these highly capable systems is possible only if we eliminate the last vestiges of human involvement with the process.

Isolation technology might be the right place to start. Isolator systems that can be reproducibly decontaminated and maintained under a continuous differential pressure to the surrounding environment represent the best available technology for aseptic processing. As mentioned, the acknowledged weakness of isolators relate primarily to the use of gloves, which are subject to breaching that can lead to contamination of the aseptic field that exists within. What if we were able to design a system with even less reliance on human intervention than we presently have in isolators? The equipment would be highly automated

and specifically designed to operate without human access and would include operating capabilities and features such as:

- provision for all routine interventions;
- eliminating nonroutine interventions;
- clean-in-place or sterilize-in-place capabilities for all product contact surfaces;
- weight verification or adjustment on all containers;
- container integrity control and confirmation on all containers;
- continuous monitoring of critical process variables;
- the use of process analytical technologies (PAT) where appropriate;
- a automated in-feed and discharge of components without human intervention;
- a automated environmental monitoring of isolator internal air and surfaces;
- a automated setup and transition from clean-in-place or sterilize-in-place to aseptic filling;
- self-clearing filling systems (for jam-free operation);
- No-container, no-fill to eliminate spillage.

These design features and others like them would allow an aseptic filling isolator to be operated without human intervention and would eliminate the need for gloves or half-suits to service the equipment. In addition to the aseptic filling and isolator elements described, such a system would likely require components of consistently high quality to minimize difficulties associated with container flaws. Systems with all of these features and more are available today and have been used in aseptic processing industries since the late 1990s.

Aseptic processing tomorrow

We must recognize that continued pressure to improve today's already good aseptic processing performance will be driven by:

- limitations of any system that uses personnel (even isolators)
- FDA's unambiguous statements regarding eliminating patient risk
- FDA's strong support for advanced technologies for improved process control.

Continued technological improvement, beyond what is commonplace today, is perhaps the only real way to achieve continued improvement. Meeting future regulatory expectations for truly sterile aseptic products will require a broad application of advanced technologies that allow operation without personnel (addressing the contamination potential) and advanced process control and monitoring (providing increased confidence in the process). We cannot attain conditions in which action levels are impossible unless we can operate without humans. The use of isolator systems, representing the pinnacle of today's technology, is not enough. Recently there has been a great interest in RABS in part because of validation and ergonomic concerns related to isolator technology. Gloves used in RABS environments, however, will not escape the issues that have arisen regarding isolator gloves. Furthermore, it is hard to see how a system that may facilitate intervention and operator involvement reflects a step forward in the evolution of aseptic technology.

The future most likely lies in the path already trod by other

industries: less reliance on manual operations and a greater reliance on electronics—a automation and robotics. Incremental improvements in aseptic processing have resulted in very safe products produced in human-scale clean rooms. Isolators and other advanced systems have improved aseptic processing beyond that. However good current performance levels are, we will be forced to go further, and we should do so voluntarily. The complete elimination of human-derived contamination is possible only with the elimination of human intervention. Technologies to eliminate personnel in aseptic processing are already available; they only need to be integrated into a total system design.

"We have met the enemy and he is us!" (Pogo)

References

1. J. Agalloco and B. Gordon, "Current Practices in the Use of Media Fills in the Validation of Aseptic Processing" *J. Paren. Sci. Tech.* **41** (4), 128–141 (1987).
2. J. Agalloco, J. Akers, and R. Madsen, "Current Practices in the Validation of Aseptic Processing—2001," PDA Technical Report #36, *PDA J. Pharm. Sci. Technol.* **56** (3), 2002.
3. H. Avallone, FDA Field Investigator Training curriculum, circa 1985.
4. Food and Drug Administration, *Guideline on Sterile Drug Products Produced by Aseptic Processing* (FDA, Rockville, MD, 2004).
5. PQRI Aseptic Processing Working Group—Final Report, 2003. <http://www.pqri.org/aseptic/images/pdfs/finalreport.pdf>.
6. J. Sharp, "What Do We Mean by Sterility," *PDA J. Pharm. Sci. Tech.*, **49** (2), 90–92 (1995).
7. WHO, "Sterility and Sterility Testing of Pharmaceutical Preparations and Biologicals," WHO/BS/73.1062 and WHO/PHARM/73.474, 1974.
8. Food and Drug Administration, *Guideline on Sterile Drug Products Produced by Aseptic Processing* (FDA, Rockville, MD, 1987).
9. J. Agalloco and J. Akers, "Current Practices in the Validation of Aseptic Processing—1996," PDA Technical Report #24, *PDA J. Pharm. Sci. Tech.*, **51** (2), supplement (1997).
10. J. Agalloco, J. Akers, and R. Madsen, "Current Practices in the Validation of Aseptic Processing—2001," PDA Technical Report #36, *PDA J. Pharm. Sci. Technol.* **56** (3), 2002. **PT**