Closed Systems and Environmental Control: Application of Risk Based Design

James Agalloco
Agalloco & Associates

Introduction

In September 2002, FDA announced its risk based CGMP initiative, the goal of which is to focus FDA compliance activities [1]. The intended effect of that initiative is to focus activities within operating firms on those activities, processes and systems that present the greatest risk to the patient. The implementation of the initiative across the industry is still evolving and has been described in additional FDA publications. Consistent with FDA's long standing policies, these publications broadly outline what firms should consider rather than detail how it is to be accomplished.

The production of therapeutic products often entails the use of closed systems where dissolution, crystallization, storage and other operations are carried out entirely within the process equipment. Requirements for equipment design and environmental control have been outlined by FDA, EMEA and industry [2,3,4,5]. Surprisingly, a system that complies with all of the prevalent regulatory expectations has some inherent difficulties that can have adverse effects on product quality. This effort will review aspects of facility design where seemingly parallel goals have inadvertently introduced risk due to added operational problems.

Excessive Expectations

The environmental conditions utilized for pharmaceutical production operations are only rigorously defined for sterile products and are primarily intended for aseptic filling operations [6,7]. Requirements for the earlier steps in these processes are less rigorous. Many of these early process steps are performed in equipment that is sterilized prior to use and is generally considered closed [8,9]. Nevertheless, contemporary facility designs for these operations: fermentation, purification, sterile bulk processing, and others, have utilized classified environments. The adoption of a classification scheme for these environments is routinely associated with process control test acceptance criteria for microbiological contamination. The acceptance criteria chosen for these environments are nearly universally the same as those used in conjunction with aseptic processing operations. While there is no requirement to do so, this choice is made in the absence of alternative standards for these less critical environments [10]. The adoption of aseptic environmental levels for these other processes has substantial implications in both equipment and facility design.

Processing equipment that is steam sterilized in-situ prior to use will be fitted with condensate lines that are hard piped to condensate return headers. This design element is intended to eliminate the release of condensate to the surrounding room. The unintended consequence of this design in many cases is to create an interactive system in which effective sterilization can be impaired [11]. Greater consideration should be given in the design to the relative risks associated with the conflict between proper sterilization of the product contact equipment and protection of the external environment. Certainly, the requirements for sterilization should not be abrogated to protect the environment where materials are not present. Wherever closed systems are a part of the facility design, their presence should obviate the need for undue concern over the room surrounding that system.

Closed Systems

Closed systems have been mentioned by both FDA and industry, with the clearest definition provided in PDA TR# 28 [12]. The features that define whether a system is closed include:

- Is sterilized-in-place or sterilized while closed prior to use using a validated procedure
- Is pressure and/or vacuum tight to some predefined leak rate maintained through the length of the campaign
- Can be utilized for its intended purpose without breach to the integrity of the system
- Can be adapted for fluid transfers in and/or out while maintaining asepsis
- Is connectable to other closed systems while maintaining integrity of all closed systems (e.g., Rapid Transfer Port, steamed connection, etc.)
- Is safeguarded from any loss of integrity by scheduled preventive maintenance
- Utilizes sterilizing grade filters for sterilization of process streams that are integrity tested and traceable to each product lot.

Where such a system is utilized for pharmaceutical processing, contamination originating in the surrounding environment is extremely unlikely to result in contamination of the materials contained within the system. Unless the materials inside the system are sterile, con-

cerns for the environment are misplaced relative to those for the materials in the system. Fermentation, purification and other processes early in the process should not be placed at risk due to compromised steam sterilization. Condensate lines from steam traps should be allowed to vent freely into the surrounding room. This affords greater reliability of sterilization, which will have far more impact on product quality than an environmental excursion in the room. It is inappropriate to risk the loss of in-process materials in order to comply with overly restrictive microbiological criteria. Only sterile materials require conformance to the microbial limits cited by regulators [13,14].

What about those closed systems where the internal materials must remain sterile? Should the same considerations apply relative to the internal and external environments? Despite what might seem to be a greater potential concern regarding external environmental conditions when the process materials must be sterile, the situation is essentially unchanged. Sterile materials must be maintained, thus no compromise of the sterilization design should be tolerated in order to protect the environment. Thus the systems themselves must be protected first, since they are designed to hold and maintain sterile materials. Worrying about the introduction of contamination into the environment from the equipment must play a secondary role since concern for the environment is ultimately only relative to its potential to introduce contamination into the equipment. If the environment is contaminated in an effort to protect the product, then the relative risks are being considered properly.

A very similar situation presents itself where equipment design is not constrained by facility concerns. Isolators, autoclaves, lyophilizers and many other pieces of process equipment contain sterile materials. Properly designed and operated this equipment is largely unaffected by the surrounding environment.

Interactive Systems

Engineers responsible for the control of dynamic processes recognize that interactive systems entail unique concerns that can adversely affect the process. Steam sterilization-in-place requires the removal of air and steam condensate throughout the process to ensure full effectiveness [15]. Where multiple condensate lines are combined into a single line prior to discharge from the system, sterilization can be inhibited. This feature can also be seen outside the system where condensate lines from multiple steam traps are hard-piped into a common condensate return. This situation is aggravated if the condensate return system is tightly sealed and/or requires a booster pump. As successful sterilization-in-place is known to be highly sensitive to condensate retention, any part of the system configuration that inhibits condensate removal should be avoided [16,17].

The surest way to avoid interaction is to allow each condensate outlet from the system to dispense directly into the surrounding environment with an atmospheric vent. The importance of this for steam sterilizers was formally noted in the now withdrawn FDA LVP guidance [18]. Universal application for closed systems would allow steam and water to discharge into the surrounding environment. This practice is almost universally objected to when the system is installed in classified environments, unfortunately to the detriment of the SIP process. The location of sterilized systems in unclassified areas is not without precedent. The brewing industry routinely locates fermentation equipment in un-classed environments and discharges steam wherever it is collected. Many of the original fermentors used for antibiotic production in the early years of this industry were similarly located and operated successfully for many years. Many of these systems are still in daily use across the industry. Contamination in either of these applications is predominantly associated with failures of either the SIP process or during transfers of sterilized materials from other closed systems. If these systems can be successfully operated without undue concern for the surrounding environment, then comparable systems that must be sterilized in-situ should be treated similarly. Protecting the environment at the risk of compromising the sterilization of closed systems skews the risk assessment entirely in the wrong direction.

Case Studies

Perhaps the best way to explain the excessive attention paid to environmental conditions relative to equipment design and operational practices is to review a number of case studies drawn from real-life situations.

Liposome Production

In considering the design of a large scale liposome production facility requiring a number of different sterile vessels, each of these would be steam sterilized in-situ. Early in the design phase, a member of the compliance staff insisted that the new facility be entirely within a Class 10,000 environment. This position was taken despite the successful preparation of clinical materials using equipment located in an unclassified environment. The firm's prior experience with the product and SIP notwithstanding, the constraints imposed by compliance remained in place. Cost estimates for a fully classified facility proved excessive, and the facility was never built. The process was later commercialized by another firm without the imposition of Class 10,000 for all of the operations.

Liposome Production

During the execution of media simulations for its liposome process, a firm encountered contamination in repetitive trials. In investigating the cause of the contamination, it was determined that the contaminating organism was routinely isolated within the CIP system. The CIP and SIP systems shared a common hard-piped header that received the effluent from both. Once these systems were separated, process simulation was successfully accomplished. The continued use of a hard-piped SIP header was mandated by the Quality Assurance department that cited FDA expectations as justification for protection of the Class 100,000 environment.

Biotechnology Production

As its products approached commercialization, a biotechnology firm decided to review its environmental control practices for all of its operations. The activities under evaluation were: fermentation, purification, media preparations, component preparation, aseptic filling, and sterility testing. A comprehensive plan was developed which acknowledged that rooms of similar particle classification could have different microbial process control acceptance criteria based upon the criticality of the processes performed within. An ex-FDAer, serving as a consultant to the firm, critiqued the program and forced the firm to adopt criteria derived from aseptic filling operations for all of its activities. The firm has suffered from a large number of excursions (followed by investigations and deviation reports) in the less capable (and less critical) environments ever since.

Biotechnology Production

A firm experienced frequent loss of in-process material due to extraneous microbial contamination. At the same time, the operation staff spent an inordinate amount of its time attempting to correct environmental excursions. It utilized a common header for steam condensate that eventually fed a remote collection vessel. The contaminating organism was detected in the lines leading to the collection vessel. Changes to the condensate return system to minimize back pressure were implemented that resulted in the elimination of the contamination problem. The environmental conditions in the room were not changed, and were never a factor in the contamination problem.

A Very Similar Concern

Isolators are closed systems, where a similar circumstance to that described above is commonplace. Much has been made of the need

to operate aseptic processing isolators in Class 100,000 environments or better [19,20]. This type of cautionary guidance overstates the risks associated with contamination induction from the environment to the isolator internals. A properly decontaminated isolator provides an internal environment superior to that attainable by any manned cleanroom [21]. Worrying about environmental controls in the room surrounding an isolator is an exercise in wasted energy. Cleanrooms have been the prevalent means for the production of sterile products for much of the last half century. Unlike isolators that are constrained to installation within Class 100,000 environments, cleanrooms are not subject to similar requirements. When one considers that Class 100 cleanrooms are often immediately adjacent to non-classified spaces and that sterilizers and lyophilizers have only one surface in a classified environment, the requirements for isolators are certainly overstated.

The apparent concern is two-fold: first, potential entrainment during operation in an open mode; secondly, introduction of contamination after maintenance immediately prior to decontamination. These fears fail to recognize the realities of isolator design as compared to manned cleanroom operations. Consider the following:

- Cleanrooms operate at comparable or lower differential pressures.
- Cleanrooms have never been subjected to leak testing in the manner of isolators.
- Cleanrooms are often adjacent to unclassified environments and in some cases discharge through 'mouse holes' in the same manner as isolators.
- Cleanrooms are rarely fitted with emergency power, guillotine devices or other mechanisms designed to protect their interior in the event of a sudden power outage.
- Cleanroom duct work is routinely located in interstitial uncontrolled spaces and is not subjected to leak testing.
- Other items of sterile processing equipment, i.e., autoclaves and lyophilizers have a substantial portion of their piping in unclassified machine areas.

The requirements for classification of the area surrounding the isolator are intended to prevent contamination from the surrounding environment from entering the isolator. This can occur either during ordinary use or during maintenance when the isolator's air system is not functioning. Protection of an open isolator from ingress of contamination is generally easily accomplished during operation by any number of design features. The performance of maintenance on any item in what is expected to be an aseptic environment must be followed by a thorough cleaning and disinfection prior to use.

The failure of a firm to consider this after maintenance on the isolator internals is a poor practice that should be corrected procedurally, rather than 'corrected' by an excessive design requirement.

However unlikely the potential for the introduction of contamination into the isolator from the surrounding environment, the imposition of a classification requirement will not alter the corrective actions required in the event of a compromise to the isolator's integrity. Proven contamination from a manned Class 100,000, or even a Class 100 environment must result in rejection of exposed materials in the isolator. Given that open isolators are predominantly used for aseptic processing, there is no acceptable circumstance under which a compromise to the system's integrity could be accepted regardless of the surrounding classification. The presence of a classified environment surrounding the isolator actually introduces the same concern that the FDA itself has indicated regarding their application, "However, users should not adopt a false sense of security with these systems" [22]. If the FDA were to believe in its own guidance, it would recognize that classifying the external environment provides no additional safety to the materials being processed. A proper risk assessment would recognize the futility of trying to make any environment outside the isolator acceptable in the event of a system malfunction.

Recommendations

Regulations impacting the design of pharmaceutical systems and equipment must reflect a true and careful consideration of the risks associated with the design. There is no "free lunch." Blindly taking the most rigorous (risk averse) approach to the design details does little more than increase both capital and operational costs, which are added to the cost of medicines. Over-design of environmental systems has already resulted in situations where end product quality has been compromised in order to satisfy the substantially less important aspects of environmental quality in environments where the product is not at risk. The industry, especially those involved in the design and operation of these systems must insure that the relative risks to the patient are properly addressed. The best design is one that focuses on product protection and recognizes the lesser need to protect the indirect surrounding environment.

Jim is President of Agalloco & Associates, a consulting firm to the pharmaceutical and biotechnology industry. He was previously employed at Bristol-Myers Squibb, Pfizer and Merck. Jim holds a B.S. and M.S. in Chemical Engineering and an MBA in Pharmaceutical Studies. He is a past PDA President and Director. He is a frequent author and lecturer on sterilization, aseptic processing and process validation. Correspondence should be addressed to: jagalloco@aol.com

1. FDA, Pharmaceutical CGMP's for the 21st Century: A Risk Based CGMP Approach, September 2003.
2. FDA, "Guide to Inspection of Sterile Drug Substance Manufacturers," 1994.
3. FDA, "Draft Guidance on Sterile Drugs Products Produced by Aseptic Processing", September 2003.
4. EU CGMP, Annex 1, Sterile Medicinal Products, May 2003.
5. PDA, "Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals", PDA Technical Report #28, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 52, No. 4, supplement, 1998.
6. FDA, "Draft Guidance on Sterile Drugs Products Produced by Aseptic Processing", September 2003.
7. EU CGMP, Annex 1, Sterile Medicinal Products, May 2003.
8. Agalloco, J., "Sterilization In Place Technology and Validation", chapter in Validation of Pharmaceutical Processes: Sterile Products, edited by J. Agalloco & F. J. Carleton, Marcel-Dekker, New York, 1998.
9. PDA, "Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals", PDA Technical Report #28, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 52, No. 4, supplement, 1998.
10. Agalloco, J., "Qualification and Validation of Environmental Control Systems", *PDA Journal of Pharmaceutical Science and Technology*, Vol. 50, No. 5, 1996.
11. Agalloco, J., "Sterilization In Place Technology and Validation", chapter in Validation of Pharmaceutical Processes: Sterile Products, edited by J. Agalloco & F. J. Carleton, Marcel-Dekker, New York,1998.
12. PDA, "Process Simulation Testing for Sterile Bulk Pharmaceutical Chemicals", PDA Technical Report #28, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 52, No. 4, supplement, 1998.
13. FDA, "Draft Guidance on Sterile Drugs Products Produced by Aseptic Processing", September 2003.
14. EU CGMP, Annex 1, Sterile Medicinal Products, May 2003.
15. Agalloco, J., "Sterilization In Place Technology and Validation", chapter in Validation of Pharmaceutical Processes: Sterile Products, edited by J. Agalloco & F. J. Carleton, Marcel-Dekker, New York,1998.
16. Kovary, S., Agalloco, J., Gordon, B., "Validation of the Steam-in-Place Sterilization of Disc Filter Housings and Membranes", *Journal of Parenteral Science and Technology*, Vol. 37, No. 2, 1983.
17. Agalloco, J., "Sterilization In Place Technology and Validation", chapter in Validation of Pharmaceutical Processes: Sterile Products, edited by J. Agalloco & F. J. Carleton, Marcel-Dekker, New York,1998.
18. FDA, Current Good Manufacturing Practices - Large Volume Parenterals (proposed), 21 CFR, Part 212, June 1, 1976.
19. FDA, "Draft Guidance on Sterile Drugs Products Produced by Aseptic Processing", September 2003.
20. PIC/S, Isolators used for Aseptic Processing and Sterility Testing, PE 004-1 (Draft 4), April 2002.
21. PDA, "Design and Validation of Isolator Systems for the Manufacturing and Testing of Health Care Products", PDA Technical Report #34, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 55 No. 5, 2001.
22. FDA, "Draft Guidance on Sterile Drugs Products Produced by Aseptic Processing", September 2003.