ENVIRONMENTAL TESTING & MONITORING:
Deciphering Compliance Requirements for
Pharmaceutical and Medical
Device Manufacturers

By Scott Mackin
ENVIRONMENTAL TESTING & MONITORING: Deciphering Compliance Requirements for Pharmaceutical and Medical Device Manufacturers

ABSTRACT

Industrial sterilization and contamination control programs are critical in pharmaceutical and medical device manufacturing. This article reviews the key elements of a best practice environmental testing program, including sterilization standards, FDA requirements, and the critical factors in maintaining controlled environments. In this paper, the author draws on his extensive experience assisting clients with program development. He reviews strategies that range from the essentials of compliance to budget development and management.

CHALLENGES FACING MANUFACTURERS — JUST WHAT IS REQUIRED?

Having assisted scores of medical device manufacturers in designing, implementing, and maintaining both their sterilization and environmental monitoring programs, we have found that the biggest challenge for the manufacturer is determining what exactly is required for compliance.

For parenteral manufacturers, the environmental control parameters are highly stringent. The collaborative effort between the Office of Compliance in the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Office of Regulatory Affairs (ORA) has produced and continues to develop the guidance for industry "Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice"[1]. While the primary focus of the guidance is on cGMPs in 21 CFR 210 and 211, considerable attention has been given to environmental control. USP <1116> “Microbiological Evaluation of Clean Rooms and Other Controlled Environments”[2] also offers these manufacturers guidance that can be used as a framework for development of programs for personnel training and environmental monitoring. The informational chapter also reviews guidelines, equipment, and statistical methods which have been adopted as industry standard. The PDA TR13 “Fundamentals of a Microbiological Environmental Monitoring Program” document is also a mainstay and offers solid guidance to all categories of manufacturers.

Conversely, device manufacturers have historically been forced to piece together a coherent and defensible strategy by choosing bits and pieces from an array of different standards, guidance documents, and corporate policies. For anyone other than a device manufacturing veteran, the task is daunting, and many times there is no concrete program implemented. Frequently, when programs are implemented, there is little confidence in their practicality or regulatory muster. When production operators do not buy into the value of the program, it often transitions to a system of documenting control failure rather than a program that demonstrates continued control and compliance. Drift from a state of control at any point within the program will likely negatively impact the entire system ultimately resulting in loss of production.

Typically, larger companies will already have solid programs in place for commissioning new production areas, continued monitoring, and sterilization validation. Additionally, since many of these companies are experienced in satisfying a variety of regulatory environments to market their products globally, their programs tend to be more comprehensive. Fortunately for Microtest, the quantity and range of controlled environments, and the associated variety of activities they are used for, has given us an advantage in continued improvement to associated systems. We have a unique understanding of a wide range of regulatory environments and applications, enabling us to seamlessly identify and respond to the day-to-day challenges encountered by our staff and clients.
PARTICULATE CHARACTERIZATION: VIABLE VS. NON-VIABLE

Since the early days of Federal Standard 209 (FS 209), cleanliness classes have been assigned to clean zones using measured levels of non-viable particulates. Initially, microbiologists and regulatory professionals struggled to draw some correlation between the levels of non-viable particles and viable particles present in the environment. But a general consensus was reached acknowledging that no direct relationship could be defined. However, because of the relative ease and practicality of continuous monitoring for non-viables it remains the most reliable method for real-time assessment of environmental control.

For anything other than the Class 100 (ISO Class 5) area, determining what satisfies the microbial sampling requirement called out in many standards is often an ambiguous matter. There are no commonly accepted levels of environmental bioburden, especially in Class 10,000 (ISO Class 7) and 100,000 (ISO Class 8) areas. Since FS 209 has been sunset and the ISO 14644 series of documents have taken its place, ISO 14644[^3] is currently recognized as the worldwide standard for designing and validating controlled environments. The drafting of the ISO 14698[^4] series of documents has provided manufacturers with concrete guidance in setting up the microbial portions of their programs. Still, the ISO 14698 (microbial) document stops short of providing a definitive method for determining just how much microbial sampling is sufficient. Many manufacturers elect to utilize the same calculation for their microbial sampling that is set forth in 14644 to sample for non-viable particulate. Even so, this still leaves the questions of what sample locations in the environment are most critical and what type of organisms (aerobic, anaerobic, fungal) must be recovered. This is open to interpretation and written justification must be provided in the overall environmental monitoring plan.

Unfortunately, as sterilization validation programs rely more and more upon bioburden control and monitoring, this missing piece becomes even more critical. At Microtest, we have been fortunate to have the opportunity to collect and analyze volumes of data that correlate environmental bioburden, product contamination, and sterilization efficacy. Our off-site Environmental Services group has encountered virtually every type of manufacturing scenario imaginable. From Class 5 Fill/Finish lines to extruding, to non-wovens, to packaging — our clients benefit from Microtest’s understanding of program development for cleaning, qualifying, monitoring, and training in any environment.

SAMPLE PLANS: WRITTEN JUSTIFICATION VS. SELECTING SAMPLE FREQUENCIES AND VOLUMES FROM GUIDANCE DOCUMENTS

Regulatory agencies almost always prefer to defer to a table or calculation for determining these parameters. They provide a comfort factor. It's reassuring to point to a document during an audit. Often the manufacturer must design an environmental sampling scheme by identifying critical areas of product contact or manufacturing activities. The tendency is to err on the side of over-sampling. At first glance, this sounds like an easy solution. But for many manufacturers, it is simply not a feasible approach with respect to budgetary or personnel resources. The expense associated with purchasing, validating, and maintaining sampling equipment, plus buying supplies and training personnel often is prohibitive. Especially since many sampling schemes and/or control parameters are verified somewhat infrequently, such as quarterly or semi-annually as set forth in ISO 14644[^5] (especially in Class 100,000 (ISO Class 8) areas). For manufacturers in this group, especially smaller companies and start ups, it makes sense to outsource. There is an attractive opportunity to draw on resources and expertise that would be too expensive to staff internally.

VALIDATION: CONTROLLING COST AND VALIDATION DATA

Microtest has developed innumerable monitoring programs, internally and for clients, that are both fiscally reasonable and pass regulatory muster. The nature of our business models gives us the opportunity to continually improve through client audits of our facility. In a way, we have been able to collect our customers’ input and construct a program that emulates the best of what all of their programs have to offer. This gives our clients a great opportunity to leverage the sum of our learning. We know what works and we know what is cost effective. Consider that before a room is commissioned, it's necessary to plan for collection of data required for validation, as well as the source for that data[^1]. Vendor responsibilities and agreements need to be clearly

[^1]: ISO 14644[^6] offers an overview of important parameters of performance. It also provides guidance including requirements for start-up and qualification.
defined, managed, and documented to avoid costly retesting. For example, during HEPA filter installation, most vendors will scan the filters and seals for leaks. We are often asked to perform this service when it has already been done, adding time and expense. Having a clear understanding of the regulatory requirements and managing vendor activities effectively will shorten project timelines, reduce expenses and get production going. ISO 14644 offers an overview of important parameters of performance. It also provides guidance including requirements for start-up and qualification. Microtest is able to streamline the entire process for our customers by combining expertise with a wide range of services. We offer a tried-and-true approach that minimizes the time and stress involved with project management and completion.

CASE STUDY: STERILIZATION METHOD SELECTION - COORDINATING MULTIPLE PROGRAMS

This is probably the most common example of how environmental control can impact other programs in an organization. The method of selecting the most appropriate environmental monitoring and terminal sterilization programs should not only be a function of product materials (gamma vs. EO); it should also take the level and nature of both the environmental and product bioburden into account. Indeed there seems to be a growing awareness among device manufacturers that there is an important relationship between their environmental monitoring and sterilization programs. This is especially true given the rising popularity of using the VDmax method for sterilizing products. In fact, ISO 11137, 11737, 13409, and TIR 33 all refer to the need to have an environmental monitoring program in place.

The VDmax method for sterilization validation and control was developed by major companies in the industry. These were large, well established manufacturers with numerous historical data regarding the normal ranges of environmental and product bioburden. It was easy to document justification for using the newer method, since they could review the trends and had a good understanding of what could be considered a state of control. Experienced manufacturers could feel confident that the environmental programs they had in place were sufficient to support product bioburden control, reducing the potential of verification dosing failures. Today, we are seeing more and more start-ups and component manufacturers using the VDmax method on new product validations.

IMPACT ON COST

The above example of VDmax program integration reduces the amount of product required during quarterly dose audit testing, which in turn reduces the annual cost of product release testing. This makes the method especially attractive to start-up manufacturers. However, the method is not always the best fit for every manufacturer, especially for companies with limited experience with controlling bioburden. AAMI TIR 33-2005 clearly states that this method cannot be used when the estimated average bioburden for product is >1000 cfu. Cost and/or product savings can also quickly vanish during quarterly audits if problems due to high bioburden are encountered. It's important to remember that the verification dose is performed at an SAL of 10-1, and on a statistically smaller sample set. An influx of unobserved resistant organism can ultimately result in retests, if not revalidation to another method, even in situations where the bioburden count itself did not increase over historical levels. This makes understanding the nature of the typical bioburden as important as the levels themselves. Trending seasonal bioburden variations and identifying in-house isolates are two examples of how to gain this understanding. For situations such as these, Microtest's qualification of its MicroSeq™ system for microbial identification has proven invaluable. It is fast and cost effective — obvious advantages when considering resolution of environmental excursions.

CRITICAL FACTORS

There are a number of other factors not always obvious to manufacturers that are an integral part to any bioburden control.

Raw Materials: Precautions should be taken to ensure that external bioburden does not travel into production areas along with components and materials. These materials should typically be removed from their original shipping containers, cleaned, and stored for staging in controlled areas within or adjacent to manufacturing
suites. For example, every effort should be made to reduce or eliminate cardboard and paper products from the controlled environment. Process flow should be clearly defined and qualified. Adhering to the plan helps to avoid surprises and dealing with unknowns.

Personnel Activities and Hygiene: There should be written and posted procedures for support of operations regarding proper gowning, hand washing, and basic microbiological principles involved in minimizing contamination from manufacturing personnel and their activities. Microtest has great experience performing smoke studies to correlate airflow concepts as simple as placement of equipment and personnel and the risk of product contamination. We also commonly help clients put together protocols with pictures from smoke studies for subsequent use in personnel training. Training documentation should be in place for all personnel who will work in the manufacturing area. For example, it is common to require manufacturing personnel to execute some type of gowning validation, using touch plates or swabs, before they are deemed competent to work in the controlled environment. An understanding of what types of house garments are appropriate to the specific activities and environment is important as well. This issue can impact cost and operator performance as well as environmental bioburden.

Housekeeping: Similar to personnel hygiene, there should be written and posted housekeeping procedures and training documentation. Close attention should be paid to cleaning materials such as mop heads and disinfectants, frequency of cleaning, and documentation of cleaning activities. Microtest has worked with most commercially available disinfectants with respect to cleaning, disinfectant validation, and challenging in-house isolates. We have assisted scores of companies with cleaning efficacy studies, disinfectant rotation programs, and use-dilution expiry.

SUMMARY

Unfortunately, there is not yet a single reference document for manufacturers to rely upon to design, validate, and demonstrate room class compliance. It’s not likely that one will be drafted any time soon. As anyone who’s been involved in the validation and monitoring process knows, the task would be monumental. The ISO 14644 series and the ISO 14698 documents have eased the task enormously and are indispensable resources for manufacturers of terminally sterilized products. The key is to keep in mind at all times that the issue is all about bioburden. We must step back and look at the manufacturing process, people, and environment as a whole when drafting our validation programs. By defining traffic patterns and identifying and limiting product and personnel contact areas, we can attain a solid understanding of bioburden. Characterizing, controlling, and understanding environmental bioburden levels and trends are the cornerstones to defining and implementing a solid environmental monitoring program which fully supports sterilization validation and release activities.
About Microtest

Microtest is a leader in testing services and contract manufacturing for medical devices, pharmaceuticals, and biotechnology. Founded in 1984, the company’s expertise and flexible processes enhance product safety and security, speed time to market, and minimize supply chain disruption. Microtest’s unique single-source capability to provide testing and manufacturing solutions allows the company to support a full pharmaceutical or medical device product release. Our facilities in Agawam, Massachusetts, include state-of-the-art aseptic manufacturing areas; analytical chemistry, microbiological, and virological laboratories; Class 100 clean rooms; onsite steam and ethylene oxide sterilization, plus depyrogenation capabilities; purified water systems; and voice/data systems.

About the Author

Scott Mackin is a Project Manager at Microtest Laboratories Inc., He can be reached at 413-786-1680 or at smackin@microtestlabs.com.

References
2. USP <1116>, Microbiological Evaluation of Clean Rooms and Other Controlled Environments
3. ISO 14644, Cleanrooms and associated controlled environments: Part 1: Classification of air cleanliness
4. ISO 14698, Cleanrooms and associated controlled environments: Part 1: Biocontamination Control — General Principles and Methods
5. ISO 14644, Cleanrooms and associated controlled environments: Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1
11. VDmax: Maximum acceptable verification dose for a given bioburden and verification dose sample size.
12. Sterility Assurance Level: The probability of a microorganism being present on a product unit after sterilization