CASE STUDY

ENVIRONMENTAL MONITORING IN COMPOUNDING PHARMACIES: FACTORS TO CONSIDER

Jeff Meek
Manager of North America Sales, Healthcare Division/ Central Region Manage
~ Veltek Associates, Inc.

INTRODUCTION

Cleanroom environmental monitoring in hospital pharmacies and 503A compounding facilities has been a topic of debate over the years. The requirements for viable and total particles air monitoring outlined in USP<797> differ from the recommendations in USP<1116> and sound aseptic techniques generally anticipated by the FDA in a classified drug manufacturing area.[5] The differences between these guidance's cause a wide range of opinions about the frequency and need for viable and total particle air monitoring in hospital pharmacies and other 503A facilities. Of course, like most things the answer is never one sided and the best course for action is most likely somewhere in the middle for these facilities. In this article, we will discuss the importance of environmental monitoring for safe aseptically produced drug products, the differences in regulatory guidance, sources of contamination, strategies for implementing a program, and the equipment your facility may consider if taking more control of your monitoring program — all while saving money in the process.

WHAT IS ENVIRONMENTAL MONITORING AND WHY IS IT IMPORTANT?

For the scope of this article, we are focusing on viable and total particle air sampling, but that is not to discount the importance (and requirement) of surface, compressed gases, and personnel sampling. Environmental monitoring is a process that is used to monitor the microbial and particulate levels in a classified area. Environmental monitoring of classified areas is a critical step in determining the effectiveness of a facilities engineering controls and to prove the effectiveness of a facilities gowning, cleaning, and disinfecting procedures. The results from your environmental monitoring program are your pharmacies "report card" on just how well your overall program is implemented. Routine environmental monitoring gives the data needed to trend the environmental quality of your classified areas and act when needed.[1] EM results also provide sound scientific data to support your rotation scheme between a disinfectant and sporicidal agent. Currently, we rely on an arbitrary time frame for rotation provided by the working compendium. Is the required monthly rotation scheme sufficient specific to your facility? Based on your data trending analysis it may or may not be. Although quite an overkill, some pharmacies apply a sporicide daily for all applications. Generally sporicidal agents are more aggressive on equipment. Their elevated concentration over disinfectants is also unhealthy for worker exposure. Your EM results can support whether in fact this is necessary by determining the species generally detected. Routinely identifying the flora specific to your facility helps us to understand the potential source of the contamination whether it by people related bugs, water bourn bugs, or from outside soil to pinpoint a few. Conducting volumetric testing semi-annually will not provide the sound scientific trending data to support any decision.

SOURCES OF CONTAMINATION

There are many sources of microbial and particulate contamination in the cleanroom. These are broken down into primary and secondary sources of contamination. Primary sources of contamination such as personnel, supplies introduced into the cleanroom, and water bring contamination into the classified area. Secondary sources of contamination are where these contaminates end up settling. Examples of secondary sources of contamination are surfaces, the air, and potentially any equipment used in compounding sterile preparations within your own pharmacy. Primary sources of contamination are controlled by a combination of functioning engineering controls and meticulous personnel training in gowning, cleaning, disinfecting, and hand hygiene. Formulating a sound cleaning and disinfecting program will control secondary sources of contamination but keep in mind that cleaning and disinfecting addresses contamination after the day's activity. Simply put, if we do not let the contamination in, we would not need to address it. Naturally, all those performing routine cleaning and disinfecting should be competent to execute the facilities plan and the products selected to

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perform the task should be chosen based on efficacy, safety, compatibility, and ultimate performance for the application intended. Failure to properly execute a sound cleaning and disinfectant program well is in direct correlation to a sound environmental monitoring program. It is for this reason that a well-designed EM program is so very important to be able to identify an inappropriate level of secondary contamination and act before it leads to product contamination.

DIFFERENCES IN REGULATORY GUIDANCE

The differences in regulatory guidance are where debate happens among the contamination control community. USP<797> requires a minimum frequency of six months for viable and total particle air monitoring in ISO 5, 7, and 8 classified areas "in operation" state.[2] While USP<1116> calls for daily monitoring of ISO 5 and 7 areas, along with twice weekly monitoring of the ISO 8 area.[3] Many State Boards of Pharmacy have created their own Code for Regulations on the subject, but the clear majority also follow the USP<797> compendium guidelines. There is quite a large gap between daily monitoring and monitoring every six months. The facilities that follow USP<797> usually comply with the minimum standard and argue this is acceptable because of their shorter beyond-use dating when compared to cGMP pharmaceutical manufacturing expiration dates. Although this may be true, it is extremely difficult to develop any trending data when sampling once every six months. If the facility did not have any other need for semi-annual monitoring (e.g., new equipment, exceeded action level, suspect contamination) the facility would miss out on two entire seasons on collecting data. Depending on where the facility is located, it could be a lost opportunity to collect EM data for any solid trending analysis. For some compounders, they opine that daily sampling is not feasible, especially when many only engage in low-risk compounding. For all other compounders, the answer lies somewhere in the middle. It is important to evaluate the risk level associated with the compounding done at a facility using risk assessment tools and use this risk assessment to define the EM sampling frequency. Medium and high-risk compounding may justify more environmental monitoring to ensure accurate data is collected and appropriate actions are taken to rectify any contamination risk. If your facility determines sampling more often is an appropriate risk mitigation step, then a best practice would be to do air monitoring monthly along with increased surface sampling. This gives better trending data which can be used to improve your contamination control program.

IN HOUSE OR OUTSOURCE?

Taking ownership of one's program certainly has its benefits. The clear benefit is that you remain in full control of your own program. From implementation to execution and everything in between you have the necessary equipment to perform your own EM testing on your own time schedule. The real-time data from points you deem appropriate supports your program and helps formulate dynamic procedures based on the testing results achieved. Understandably, there will be some trepidation in bringing the program in-house. There are EM equipment manufacturers that will provide the necessary equipment and will support your program from implementation and set-up to micro identification and a suggested corrective course of action if needed. By owning the equipment outright, you know the integrity of the equipment put in use inside your classified areas that ultimately produce sterile product for patient care. Consider this, not all third-party EM companies are alike. The non-sterilizable equipment brought into your facility by outside testing firms for EM testing was previously used in other facilities. Not to mention the physical handling, storage, and transport of the unit out in the field. The fact is that much of the available equipment used inside the classified area have internal components exposed to outside air which physically cannot be wiped down with a biocidal agent. In the healthcare setting we work, it is all about risk assessment and eliminating any low hanging fruit related to potential risk which can possibly cause patient harm through compromised or adulterated sterile preparations.

The guidelines state that at a minimum, semi-annual viable testing be performed. Some operations may seek additional testing voluntarily or be mandated to perform additional tests involuntarily if micro counts exceed action levels and retesting is required. The cost for these third-party tests adds up very quickly. However, it is common to see a return on investment (ROI) in just one, or two, years' time when you compare the initial cost outlay for the necessary EM equipment compared with EM outsource testing two to three times per year. Once the facility gets over the initial planning and implementation phase of an environmental monitoring program, it becomes a routine and manageable process. With the help of a competent EM equipment manufacturer, these challenges can be easily overcome to take control of your environmental monitoring program, gather more data, and eliminate the cost of third-party environmental sampling all together.

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STRATEGIES FOR IMPLEMENTING A SAMPLING PROGRAM

When developing a sampling plan, it is important to first conduct a risk assessment to determine the sampling frequency and what points pose the greatest risk to your compounded sterile products (CSPs) and thus are most practical to sample. There are many strategies for conducting a risk assessment, here we will talk about two: one for surface sampling and the other for viable and non-viable air monitoring. The first is a touch point risk assessment where during an observation period touch points are observed, documented, and analyzed afterword to determine the frequency the surfaces were touched and if these surfaces have high enough risk to justify surface sampling. The second is a traffic flow risk assessment to determine where viable and non-viable monitoring should take place. The traffic flow risk assessment is done by observing the flow of personnel, materials, waste, and finished product. This flow pattern is analyzed to determine high-risk areas to perform viable and non-viable air monitoring. These can include the areas adjacent to pass-throughs, spaces between or bordering ISO 5 areas, and inside the ISO 5 area.[4] Partnering with the right equipment manufacturer can help you with the risk assessment process and work with you to develop a strategy to effectively use their viable and total particle air samplers.

EQUIPMENT FOR IN-HOUSE VIABLE & TOTAL PARTICLES AIR MONITORING

There are many factors when selecting the appropriate equipment for your environmental monitoring program. These can include reporting features, wireless connectivity, battery vs AC powered, the ability of the unit to be disinfected, and cost. Again, the right EM equipment manufacturer should help make the selection process easy due to their inherent knowledge of the available equipment, the necessary guidelines for use, along with practical application and knowledge of aseptic best techniques. No matter what your goals, choosing the right partner can help you select the correct product for your specific needs.

The viable EM unit for volumetric air testing most used for hospital pharmacy and 503A compounders is a handheld portable device due to its size and convenience. For classified areas, keep in mind the inherent risk of these units is that they are not sterilizable and disrupt unidirectional airflow. For these reasons, the FDA would not accept handheld units inside an ISO 5 drug manufacturing area. Their position for 503A's appear far less stringent and do not disallow this practice, provided testing is performed immediately after compounding is finished. From a risk perspective, there are EM equipment available that can draw the necessary vacuum to the atrium "head" that sits outside of the ISO 5 PEC to draw sufficient vacuum. The sterilizable head is the only component that sits inside the PEC so there is no issue of potential cross contamination or disrupted airflow.

Handheld units that are considered for the hospital pharmacy and 503A cleanroom industry should be validated for their physical and biological efficiency and provide strict regulation of air flow and alarm the operator if the air flow deviates beyond the acceptable range. The system should monitor and indicate a variety of operational parameters including the samples volume and elapsed time. Ideally, consider a network device that may be remotely accessed by operators and administrators for convenience. These devices can export event history to a removable USB flash drive which captures sampling and calibration events.

An alternative to the handheld devices for your viable air monitoring is the utilization of a standalone Control Center. These units designed for isolators are used to control calibrated and timed vacuum sequences to individual or multiple SMA Atriums (sampling points) within an isolator system. In addition, the control center for isolators provides strict regulation for airflow and will visually and audibly alarm if the proper air flow is not maintained. Control centers for isolators assure the non-aspiration or return of possible contaminates from the exterior environment to the isolator by providing connections for a purge pump.

Total particle counters for the hospital and 503A marketplace should be chosen for convenience of use and application. The typical configuration is a handheld device with the appropriate flow rate and in compliance with the ISO 21501-4, but they are also available in a table-top or wall mount design. Either way, the device should promote a large touch screen with user friendly software for ease of use. Users should be able to view data including records and reports. Data should also be easily transferred to a facility monitoring system, printer, USB, or compatible software for proper record keeping status. Data may be transferred via ethernet, USB, or wireless RS 485 and RS 232 type ports. Handheld and table-top units can usually be powered by battery or plugged directly into a charger. Wall mount models must be connected to facility power. These units are fast, efficient, and accurate. Again, the right supplier should provide guidance and direction to which unit is best suited for your specific operation.

References:
[1] ***Compounding Sterile Preparations.*** American Society of Health-System Pharmacists, 2017.
[2] USP<797> Pharmaceutical Compounding – Sterile Preparations
[3] USP<1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments
[4] Gonzalez Ramirez, Karen. *Risk-Based Viable and Non-Viable Monitoring Sampling Plan for Microbial Control Program within ISO 7 Cleanroom.* 2017
[5] Guidance for Industry – Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice.

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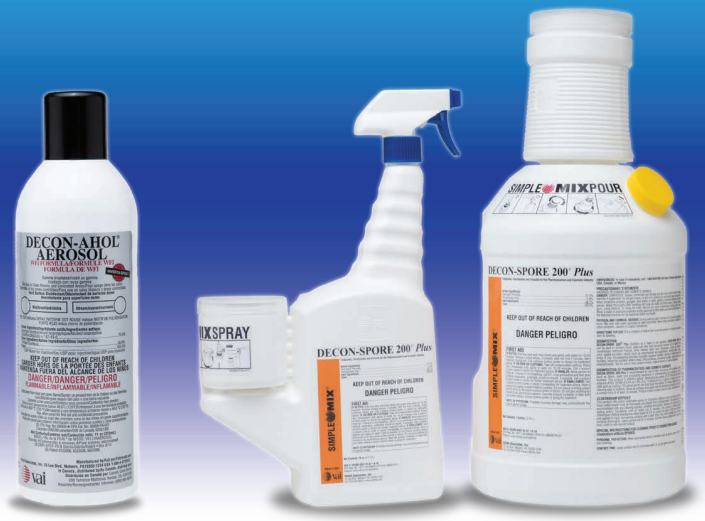

Environmental Monitoring Equipment

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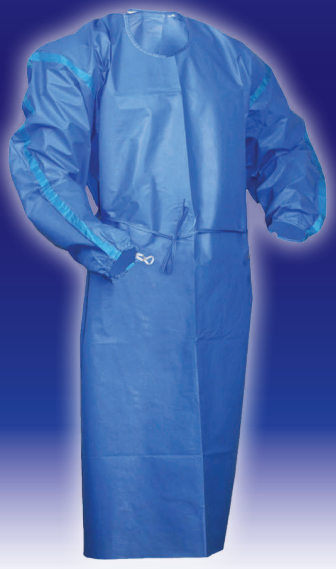
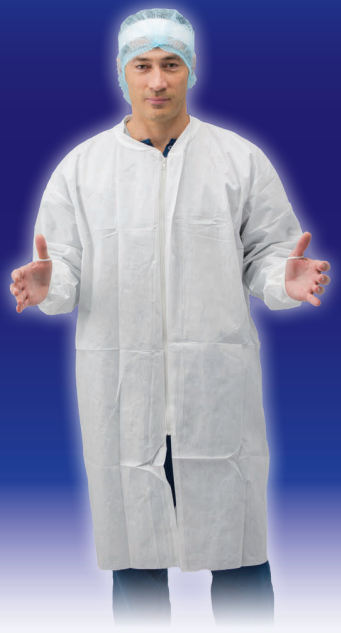


Cleanroom Garments



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