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Environmental Monitoring and Decontamination of Pharmaceutical Production Facilities

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This article reviews a facilities environmental monitoring program and the decontamination measures that might need to be added in order to achieve satisfactory results within the program.

Introduction

Environmental Monitoring and Testing of Pharmaceutical Facilities

Maintaining a comprehensive environmental monitoring program is critical to the pharmaceutical industry, as it can act as an early indication for potential contamination of products. An effective environmental monitoring program includes the sampling of microbiological risk areas within the plant to find organisms before they get into the product, and verifying that all cleaning and sanitizing procedures are working effectively. When analyzing and revising a sampling program, many questions must be answered. "What organisms (bacteria, viruses, fungi, spores) are of greatest concern?" "What are the acceptable microbiological limits for our sample results?" "Where should we take samples from?" "Is air sampling necessary?"

The first step is to understand the microorganism(s) of concern.

- What is the primary habitat? Some, like Staphylococcus and Pseudomonas, are found on people's skin, hair, nasal passageways, and mouth; or is it a soil organism (like *Bacillus spp*)? Sources can be very widespread for many microorganisms and can include "the great outdoors," ingredients, the production plant environment, pallets, drains, humans, animals, and insects.
- What nutrients and conditions (water availability, oxygen, temperature, pH, etc.) are required for the organism to grow and survive? Organisms like *Pseudomonas spp* and yeasts thrive in moist environments.
- What are the necessary steps required to kill the organism (sterilization, disinfecting solutions, fumigation)?
- Has the organism been implicated in contamination for the same or similar products? *Pseudomonas spp* has been linked with contaminations in Liquids, Ointments, and Creams (LOCs).
- Are there USP tests available to detect the organisms? Some organisms (like *B. cepacia*) are not detected by current USP tests.
- What should you be concerned with? Some bacteria have a high infectious dose in order for most individuals to exhibit symptoms (*Bacillus spp* is ~10^5 – 10^8 viable cells or spores). Others such as *Staphylococcus spp* and *Pseudomonas spp* can come from people (workers) and are easy to kill, but have the ability to quickly become resistant.

In the beginning of an environmental monitoring program review, in-depth baseline testing should be done to thoroughly understand the plant environment and location of harbors and niches where organisms reside. There are two components of an environmental monitoring program and both can be failure points: the sampling frequency and the

sampling method. Sampling methods should include air sampling, both passive and active, to measure the quantity and type of airborne organisms present. Swabbing both wide areas as well as pinpoint areas in crevices and on equipment also should be performed. During the initial environmental monitoring phase, as well as periodically thereafter, both Total Aerobic Plate Counts (TPC) as well as identifying specifically what organisms are present should be performed. This provides a good baseline of what organisms are present. Sample locations should be expanded to test the hard-to-reach areas that might not be easily accessible and might require the disassembly of some equipment and components in order to properly sample and survey them. Much like the rule of Real Estate, the rule of sampling is "location, location, location." It's important to test in as many locations as possible, including ones that have never been tested before. The goal is to have as complete a survey of the facility as possible, knowing where contaminations originate and are harbored. Once this baseline has been established, the normal cleaning and sanitizing methods should be performed. It is important that the cleaning step be performed without forewarning of the review such that the truest measure of the cleaning staff and the cleaning program are taken. Indicator organisms and biological indicators are commonly used during this step, and placed throughout the facility, allowing for a measurable result of the cleaning that was performed. Upon completion of the standard cleaning method, another round of sampling should occur and the indicators can be tested to gauge the efficacy of the established cleaning method.

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Contamination continues to be a difficult challenge for all sectors of the pharmaceutical industry and poses a significant hazard to human health. The presence of these organisms in the pharmaceutical facilities can lead to costly product recalls, which can result in loss of revenue, customers, prestige, and brand reputation. Bad publicity, expensive legal fees, increased insurance premiums, and perhaps even closure are other potential hazards of plant contamination.

Another important step in setting up an environmental sampling plan is to know your product, the target consumer group (children, the elderly, pregnant women, and immunocompromised individuals are more susceptible to bacteria induced illness), and the environment in which the drug is being produced. Certain products and manufacturing operations are more susceptible to certain microbial contaminants, making the sampling of those organisms a priority. Some processing facility attributes to consider are the following:

- Type of processing (terminal sterilization available or not)
- Plant cleaning and sanitation schedule
- Rotation of sanitizers
- Separation of production and storage areas
- Flow of product compared to worker traffic patterns
- Age and wear of equipment and facilities
- Presence of rust
- Floors, drains, roof, and overhead concerns
- Standing water
- Air handling systems and dust
- Pest control and trash management
- Sink areas

So what corrective and preventive action needs to occur if the sample results show that the standard cleaning method is not able to satisfy the requirements of the environmental monitoring program and positive samples are being found? The facility must look at the source of contamination for a possible solution (replacing equipment with more sanitary model?) or enact a more thorough cleaning step through a more aggressive cleaning agent. The frequency that the environmental monitoring program should perform sampling should be determined by the facility's management. One factor to consider when determining a sampling schedule includes the maximum production batch acceptable to recall if positive samples are found. Sanitization frequency would be determined through a similar process based on sampling results and the sanitization method's potency. If a facility's environmental monitoring results stay good for three weeks, but then positives arise after four weeks, it might be necessary to increase the decontamination frequency using the existing method or to move to a more effective method to eliminate a greater portion of the organisms initially.

High-Level Antimicrobial Cleaning Methods

The United States Environmental Protection Agency (US EPA) defines antimicrobial pesticides as substances or mixtures of substances used to destroy or suppress the growth of harmful microorganisms, such as bacteria, viruses, or fungi on a variety of objects and surfaces.

Antimicrobial pesticides have two major uses:

- To disinfect, sanitize, reduce, or mitigate growth or development of microbiological organisms
- To protect objects (e.g., floors and walls), industrial processes or systems, surfaces, water, or other chemical substances from contamination, fouling, or deterioration caused by bacteria, viruses, fungi, protozoa, algae, or slime[1]

Pesticides are classified by their levels of kill by the USEPA,[1] which are:

- ***Antiseptics and Germicides:*** used to prevent infection and decay by inhibiting the growth of microorganisms. Because these products are used in or on living humans or animals, they are considered drugs and are thus approved and regulated by the US Food and Drug Administration (FDA).

- ***Sanitizers:*** used to *reduce*, but not necessarily eliminate microorganisms from the inanimate environment to levels considered safe as determined by public health codes or regulations.

- ***Disinfectants:*** used on hard inanimate surfaces and objects to *destroy or irreversibly inactivate infectious* fungi and bacteria, but not necessarily their spores. Disinfectant products are divided into two major types: hospital and general use.

- ***Sterilizers (Sporicides):*** used to *destroy or eliminate all forms of microbial life including fungi, viruses, and all forms of bacteria and their spores*. Spores are considered to be the most difficult form of microorganism to destroy. Therefore, the USEPA considers the term Sporicide to be synonymous with "Sterilizer."

No matter what antimicrobial pesticide is used, and no matter what level of kill is desired, the following items must be achieved in order for the method to be successful:

- Good and complete distribution
- Good and total penetration
- Sufficient contact time
- Sufficient concentrations

A method cannot work if it does not contact the organism for the proper amount of time at the right concentration. No matter what the method is classified as, it will be unsuccessful if it cannot come in contact with the organism. If the method becomes diluted or breaks down quickly, it will be unsuccessful. As such, it is important to look at the methods and examine their traits to see whether it can be efficacious for your application.

There are several available methods for decontamination. The most prevalent or most common method is spraying and wiping. In this method, the user sprays a liquid sanitizer/disinfectant/sterilant around the area to coat all surfaces. While this method is the most common, it is also the most fallible. It is extremely difficult for the user to spray or wipe all surfaces within an area and keep them wet at the correct concentrations for the prescribed amount of time. For example, Luftman[2] described a facility which had a *Salmonella* contamination. In this facility, the users attempted to clean and decontaminate it on two separate occasions using a spray and wipe method, but were unsuccessful each time at eliminating the contamination. They were unsuccessful because they could not reach all the niches to fully decontaminate the facility. To eliminate the contamination at the facility, a gaseous fumigant (chlorine dioxide gas) was utilized. This method was successful in eliminating the salmonella contamination because the gas was able to reach the contamination, even in niches, and was monitored at the proper concentration for the appropriate amount of time.

Automatic foggers are another method that is used, but still has the same limitation of reaching all surfaces. In this method, an atomizer is utilized to create a fine mist of physical particles (5 to 100 microns) which then coats all surfaces. This method is subject to room geometry though, and odd shaped rooms create blind spots because of fogger equipment placement. When locating the foggers within the space, it is critical to have a line of sight to all areas in order for the disinfectant to reach all surfaces. This is extremely difficult when equipment is in the room, as mists and fogs have trouble reaching behind and below surfaces. It must be remembered that organisms are 0.5 to 2 microns in size, and can hide in niches too small for the 5+ micron mist to reach. Lack of total distribution and an inability of penetrating crevices where organisms can exist limit the effectiveness of fogging methods.

Ionized foggers attempt to overcome limited distribution by atomizing and positively charging a 7.5% hydrogen peroxide solution to allow the disinfectant to stick to negatively charged surfaces. While this helps with negatively charged surfaces, which most are, positively charged surfaces such as glass and aluminum would actually repel the ionized fog. This method still holds the same limitations of not being able to distribute to all surfaces and penetrate into crevices and niches where organisms can exist.

The limitation of reaching all surfaces is where fumigation comes into focus. For applications where it is critical to reach all surfaces (such as a plant-wide contamination with pathogenic bacteria), fumigation is the process that achieves total coverage. The fumigation methods available consist of vapors (hydrogen peroxide dry process and hydrogen peroxide wet process) and the true gases (chlorine dioxide, formaldehyde, and ozone).

Vapor Phase Hydrogen Peroxide (VPHP) is a residue-free fumigant that has been used for more than 30 years for sterilization.[3] The International Agency for Research on Cancer (IARC), National Toxicology Program (NTP), and the Occupational Safety and Health Administration (OSHA) do not list hydrogen peroxide as a carcinogen; however, the American Conference of Industrial Hygienists (ACGIH) does classify it as an A3 animal carcinogen. Typically, a 35% hydrogen peroxide and 65% water solution is boiled or vaporized and then injected into the room or target chamber. There are currently two processes for VPHP: a dry process and a wet process. In the "dry" process, the Relative Humidity (RH) is lowered to maximize the amount of vapor in the air. The vapor is maintained in the dry state to maximize distribution of the vapor. In the "wet" process, the RH is not lowered prior to injection, and the vapor is injected and allowed to condense on surfaces. Either process will have varying amounts of condensation since VPHP is not a true gas at room temperatures (hydrogen peroxide's boiling point is 109°C) and RH levels can typically exceed 90%.[4] When this condensation occurs, the concentration increases to a maximum concentration of 78% hydrogen peroxide.[5] This concentrated oxidizer can cause surface damage to painted surfaces[6,7] and epoxy surfaces.[7,8] Another drawback with VPHP is it has poor distribution[9,10] and poor penetration abilities into 5 mm gaps[11] and small tubing and openings.[12]

Gaseous methods fumigate by introducing a gas into the facility, allowing the gas to fill the space according to natural gas laws which state that a gas will completely and evenly fill the volume in which it is contained in. Gases differ from fogs and vapors in this way, as fogs and vapors are poor at achieving passive diffusion and are thus limited in their distribution. Gases, whose molecules are measured in picometers, also are smaller than fogs (5 to 100 microns) or bacteria (approximately 1 to 2 microns). Some gases used for antimicrobial fumigation are methyl bromide, ethylene oxide, formaldehyde, ozone, and chlorine dioxide gas. These gases all share the ability to distribute readily throughout a space, but there are distinguishing traits that make some unsuitable for fumigation within a facility. Methyl bromide, for instance, is recognized as an ozone-depleting substance[13] and as such is banned from most uses. Ethylene oxide is a carcinogen and is explosive at use concentrations[14] and needs to be used within special chambers using damage limiting construction. Formaldehyde is a known carcinogen[15] and also leaves a dangerous residue,[16] both of which make it ill-suited for use in a production facility. Ozone has been shown to have limited efficacy against a variety of organisms[17] and has a lifespan (20 to 30 minutes) much shorter than its contact time (multiple hours). However, Chlorine Dioxide (CD) gas is non-carcinogenic, non-residue forming, and highly effective against pathogens and microorganisms.[18,19] For this reason, chlorine dioxide gas is being used for antimicrobial fumigation within the pharmaceutical, life science, defense, healthcare, and food industries for a wide range of applications including whole facility decontamination.[2,20,21]

Gaseous fumigation methods such as chlorine dioxide gas hold a distinct advantage toward achieving high-level decontamination in hard-to-reach areas. Tall areas such as warehouses and processing tank rooms prove too difficult for vapors and fogs to reach the upper surfaces as gravity affects the fog and vapor droplets and prevents them from reaching such heights. True gases are able to reach high surfaces with no drop in concentration, offering the same level of decontamination from floor to ceiling. Gases evenly mix per the kinetic theory of gases enabling the decontaminating gas to evenly mix with the air which touches all surfaces.

Verification of the effectiveness of the decontamination also can be accomplished in various ways. For fogging, vapor, and gassing methods, biological indicators can be placed around a facility demonstrating sporicidal kill. They can range from 3 log of organisms to 6 logs depending on customer preferences. Swabbing for viable organisms also is another method that can be utilized for all decontaminating methods. For certain gases, continuous concentration monitoring exists to ensure that the cycle parameters were attained for the desired level of decontamination. This can assure that even remote areas of the facility have met the required dosage before the decontamination cycle is ended. This also will ensure that the proper dosage is attained even if a facility is not completely airtight.

Safety and use instructions, including concentrations and application rates for the organisms in question, for all decontamination methods must be obtained by reading the complete USEPA approved label instructions and used accordingly. Material compatibility should be verified when choosing a decontaminating agent. The agents also should be investigated regarding residues that might affect product. Safety data and warnings also are found on the MSDS sheets for each specific agent and should be read and followed.

In the event that a widespread contamination does occur at a facility, gaseous decontamination would prove the most effective method towards eliminating the problem. It would prove impossible to spray and wipe an entire facility, and vapors would not be able to contact all surfaces either. By filling the facility uniformly with a gaseous sterilant proven to eliminate all viruses, bacteria, molds, and spores, such as chlorine dioxide gas, a facility can be guaranteed that the microbial contamination is eliminated from all surfaces, including cracks and crevices. A whole facility decontamination can take place in as little as one day depending on the size and timeframe necessary.

Conclusion

Microbial contamination of pharmaceutical production facilities continues to be a difficult challenge for the indus-

try, and can provide a significant health hazard to human safety when disease-causing microorganisms get into the final product. Companies that have a comprehensive environmental monitoring program have an advantage toward limiting microbial contamination and its effect. A well-maintained program will include microbiological testing of the risk areas in the plant, locating the organisms before they get into the product, and also will verify that the cleaning and sanitizing procedures are effective. Once the environmental monitoring program has been made as comprehensive as possible, the sanitization plan should be reformed to meet the needs and risk areas defined by the environmental monitoring program.

If a persistent or widespread environmental contamination does occur in the facility, fumigation may be necessary as it provides a decontamination method to completely eliminate pathogens. There are many ways to decontaminate spaces. Regardless of which method is chosen, the agent or technology must achieve complete distribution, good penetration, and sufficient contact time at the required concentration. Chlorine dioxide gas is the only non-carcinogenic, residue-free fumigant which is able to reach all surfaces from floor to ceiling (including cracks and crevices) and eliminate all viruses, bacteria, fungi, and spores. With an improved sampling program and a more thorough sanitization program involving a high-level decontamination method, contamination control within a pharmaceutical facility will be able to shift to a more preventative program with less chance of widespread contamination and costly product recalls.

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