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PRACTICAL ISSUES IN DESIGNING AND IMPLEMENTING AN ENVIRONMENTAL CONTROL PROGRAM

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INTRODUCTION

There are many regulatory documents that provide guidance or regulation of environmental monitoring activities for products that are aseptically processed. Additionally, several industry groups (e.g., International Society for Pharmaceutical Engineers [ISPE], Parenteral Drug Association [PDA]) have generated publications for these processes. Other regulatory inspectors have further used these requirements as the basis for requirements for other types of processes, e.g., terminally sterilized product manufacturing, manufacturing of non-sterile products, cosmetics, and so forth. Translating these requirements or guidance into workable programs for your facility that are practical and manageable may be more difficult. This chapter discusses some of the issues faced by industry in designing and implementing these programs. In most cases, the bulk of the guidance on developing environmental control programs is written based upon aseptic processes, which is considered to be the most stringent application of these requirements. Some of the components of an environmental control program include:

- Regulations/industry guidelines/compendia requirements
- Policies and standard procedures
- Utilities

- Lab methods and supplies
- Cleaning and disinfection systems
- The systems which are monitored, e.g., air, water, compressed gases
- The limits/levels or control parameters set
- Room classifications
- Frequency of testing
- Selection of sample sites
- Personnel and training
- Culture media, e.g., recovery and incubation media
- Lab equipment
- Documentation generated and required
- Approach to data management
- Data collection and analysis tools
- Change control systems
- Data review
- Data interpretations
- Investigations/deviations/corrective actions
- Reports generated

REGULATORY EXPECTATIONS FOR ENVIRONMENTAL MONITORING

For the United States, a guidance document has been issued by the Food and Drug Administration (FDA) (1994) that identifies the type of information that must be submitted in the application to support the sterilization process validation for aseptic

processes. This document describes the information to be submitted, but does not identify how this data must be generated or collected. For example, it may require a manufacturer to describe the microbiological monitoring program used for airborne viable organisms without describing what should be included in that program. Table 2.1 provides an outline of the types of information required for submission using this guidance document.

Table 2.1 Environmental Monitoring Information to be Included in US Regulatory Submissions

- Overall description of the monitoring program utilized for routine production and media fills
- Description of the microbiological methods utilized in the environmental monitoring program, e.g., sample collection, sample transport, methods used to neutralize sanitizers, incubation procedures, and calculations of results. The monitoring program should include:
  - Airborne microorganisms
  - Microorganisms on inanimate surfaces
  - Microorganisms on personnel
  - Water systems
  - Product component bioburden
- Description of the periodic or routine methods used for yeasts, molds and anaerobes should be provided
- Description of the actions taken when specifications are exceeded should be provided

The FDA has also issued guidance on aseptic processing (1987) that includes some references to environmental monitoring. (FDA, 1987). A revision to this document was published in 2004 (FDA, 2004). This document includes an extensive discussion of environmental monitoring and describes the regulatory expectations for the program established. Table 2.2 provides an overview of the types of regulatory expectations in this document.

The European Good Manufacturing Practices (GMPs), Annex 1 (2003) also describe requirements for environmental monitoring of aseptic processes (Eudralex, 2003). In this document actual values are specified as allowable limits for microbial sampling results. These values are represented in Table 2.3.

Table 2.2 Overview of Regulatory Expectations Described in the Aseptic Processing Guidance

- Well-defined, written program that uses validated methods
- Covers all production shifts
- Includes air, floors, walls and equipment surfaces, including critical surfaces that come into contact with product containers and closures
- Risk-based sampling frequency and locations
- Scientifically sound principles used:
  - Sampling procedures
  - Standards
  - Test limits
- Sample sizes sufficient to optimize detection of environmental contaminants at the levels that might be expected in a clean area
- Written list of sampling locations
  - Samples should be taken throughout the classified areas of the aseptic processing facility
  - Air and surface samples taken at locations where siginificant activity or product exposure occurs during production
  - Critical surfaces should remain sterile
  - Critical surface samples taken at the conclusion of the aseptic process
- Standard Operating Procedures (SOPs) should include:
  - Sampling locations (defined for reproducible sampling)
  - Sampling frequency, time of sampling (during or end of production), duration of sampling and sample size (e.g., surface area, air volume)
  - Specific sampling equipment and techniques
  - Alert and Action limits (levels) established
  - Appropriate responses to deviations from established limits (levels)
- Each individual sample result should be evaluated for significance by comparison to the Alert/Action levels
- QC should provide routine oversight of trends in data (short and long-term)

Table 2.2 Continued

- Trend reports should be generated by:
  - Location
  - Shift
  - Room
  - Operator
  - Or other parameters, e.g., where a certain isolate was found in the facility
- Trending
  - Don't only consider repetitive counts an adverse trend
- Written procedures defining how responsible managers are informed and updated on trends and investigations
- Guidance identifies expected Action levels for both viable and non-viable particulates

Table 2.3 Excerpted Environmental Monitoring Limits from EU GMPs, Annex 1

	Recommended Limits for Microbial Contamination (a)			
Grade	**Air Sample cfu/m³**	**Settle Plates (diam. 9.0 mm), cfu/4 hours (b)**	**Contact Plates (diam. 55 mm), cfu/plate**	**Glove Print 5 fingers cfu/glove**
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	–
D	200	100	50	–

Notes:
(a) These are average values
(b) Individual settle plates may be exposed for less than 4 hours

Some regulatory organizations (internal or external to the company) require compliance to the International Organization for Standardization (ISO) or other standards.

PRACTICAL ISSUES IN DESIGNING A CONTROL PROGRAM

There are a variety of issues that one may need to confront in designing and implementing an environmental control program. The issues covered are only a taste of the issues facing the personnel who establish these programs.

Cleaning, Sanitization and Disinfection Procedures to be Used

Establishment of a cleaning and disinfection program requires a basic knowledge of the number and type of organisms present in a facility. Once baseline data for the normal environmental flora is obtained, one can work with vendors of cleaning and bio-decontaminating products to determine what sanitizers, disinfectants and sporicidal agents may be used. A variety of products exist, each with advantages and disadvantages that must be considered when establishing a cleaning program.

Part of the selection process involves determining which surfaces to be cleaned are the most difficult to clean, which organisms present in the environment are the most resistant to each cleaning agent to be used, and what contact time is required to inactivate the most resistant microorganism on the most difficult to clean surface. After this data has been collected, a cleaning regime can be established.

One must take into consideration:

- Method to be used to apply the cleaning agent/sanitizer and disinfectant
- Safety and personnel issues associated with the selected cleaning agents
- Cost
- Effects of the cleaning agent on the surfaces to be cleaned, e.g., are they corrosive to stainless steel
- Product interactions to the cleaning agents

Finally, the methods and procedures to be used are validated, testing the surfaces before and after cleaning to determine the effectiveness of cleaning.

Standards to be Applied

One of the first issues that must be addressed for facilities is determining the standards to be applied. The trend is for pharmaceutical companies to do business on a global basis. It may be difficult to determine all of the requirements that must be met. These

standards may be established by both sources internal and external to the company. Even the nomenclature used to define classifications of air cleanliness in rooms is different between the various standards that exist, e.g., Grade A, ISO 5, Class 100. For this reason, there are companies that have chosen to abandon the specified classifications and who have used colors or other names as room classifications. This has allowed them to establish levels that may reflect the 'harmonized' values for several standards, while having requirements that may not match any one of these standards exactly. Other companies may choose to use closely related values as if they are equivalent, e.g., Class 100/ISO 5/Grade A.

Identification of the Room Classification Required for Each Area

Some areas, e.g., the filling area in an aseptic process, may be very easy to classify. Other areas are not so easily classified, e.g., the filling area for a terminally sterilized product. One may need to review the regulations for all countries where products will be marketed. Some regulations may require that aseptic filling be performed, but others may not require aseptic filling. If the room does not have to meet regulations for aseptic filling, what room classification, if any is required? It is useful to have a site policy or master plan that defines how these classifications are determined.

Selection of Sampling Methods and Equipment

There are many standard methods used as part of an environmental monitoring program. Sampling for airborne viable microorganisms may be performed using any one of a variety of different systems, from fall-out plates or media that are qualitative methods (passive air monitoring), to quantitative methods that sample a known volume of air, deposit the microorganisms present on an agar surface or filter, and then can be enumerated (active air monitoring). Subsequent chapters in this book describe the various sampling devices that are available. Each system available has both advantages and disadvantages. While most if not all of these systems can be used, each company must weigh the good and the bad and select a system that works best for them. There is a regulatory expectation in the United States (FDA Aseptic, 2004) for both active and passive air monitoring. In addition to selecting a specific type of equipment to use for sampling, one has the ability to choose a portable unit that is moved or carried to the sample site each time a sample is collected, or to use a permanently installed unit. Other features may also be important, e.g., whether the unit can be sterilized, sanitized, or disinfected.

Sampling of non-viable particulates is also performed using instruments designed for this purpose. Both portable and in-line systems are available. The number and type of units required, the level of validation support provided for the hardware and software, and the type of system are all considerations in selecting equipment for use.

Surface sampling (and personnel monitoring) are typically conducted using Replicate Organism Detection and Counting (RODAC™) media. In some cases, flexible films, swabs or rinses may be used. As stated for other methods, it may be necessary to weigh the advantages and disadvantages for each system available.

Rapid microbiological methods, also known as alternative methods, may also be used for environmental monitoring. Several systems are available and are discussed later in this book. Another consideration for automated systems is the throughput necessary for environmental tests. Typical pharmaceutical facilities may have several hundred or thousand samples collected and processed on a daily basis. Many of these automated methods are limited in the number of samples that can be processed each day, and this should be addressed prior to purchase of a system for use.

Incubation and Recovery Conditions

After sampling methods have been selected, one must also consider how the samples will be incubated during the test methodology. Some companies collect duplicate samples using two different media. One media is for fungal recovery, while the other is for bacteria. Each of the media is incubated at a different temperature for the type of organism to be detected.

Other companies choose to use one type of nutrient agar or broth and to use a bi-phasic incubation condition, e.g., incubating at 20–25°C for a specified number of days followed by incubating at 30–35°C for another specified number of days.

Another group of companies vary this procedure by generating data to show that one temperature and one media fits all the needs of the environmental control program, e.g., they may use the single media and incubate at only one temperature for the entire time period, e.g., 30–35°C.

In addition to specifying the incubation conditions used, one must identify the type of media that will be used for recovery. Most environmental isolates in a pharmaceutical environment are stressed and they may not exhibit the same level of growth on different media. For example, a large amount of data has been generated on R2A media and Trypticase Soy Media for monitoring of water. Since the organisms that are typically present in water live in areas with very minimal nutrients, placing them on a media that is high in nutrient content may be more difficult for the organisms than placing them on a minimal nutrient media, e.g., R2A. This is analogous to taking people who are starving and feeding them a huge meal. In most cases, they cannot handle such a drastic change in eating habits in such a small period of time. It may be much more effective to make small changes, starting with eating small, simple meals and advancing to more substantial meals. Literature or data should be used to support the media and incubation conditions selected.

Validation of Methods

Many of the environmental monitoring methods utilized may be validated. Some companies feel that because these methods have been in long term use, qualification of the method is sufficient. There is guidance available for validation of the recovery of microorganisms in the United States Pharmacopeia (USP) (USP 26 <1227>, 2003). PDA Technical Report Number 13 (Revised), *Fundamentals of an Environmental Monitoring Program* also provides guidance on the validation of environmental monitoring systems. For rapid microbiology methodology, USP has a draft chapter <1223> for the validation of alternative microbiological methods (Pharmacopeial Forum, 2003). PDA also has a technical report that describes the purchase, validation and implementation of these types of systems (PDA, TR 33, 2000).

There are several issues with validation or qualification of some environmental monitoring methods. For example, when a company changes from one viable air monitoring device to another, the technology used for monitoring may be very different. As such, even data collected in matched-pair or side-by-side studies may be of limited value. Unfortunately, this is the methodology used most frequently to assess a change in equipment.

Passive monitoring methods are impossible to validate or qualify, since there is no quantitative method being used. The most that can be done is to ensure that the selected media is growth promoting, and for solid agar, one would need to show that the plate does not dry out or lose its growth promoting capability during the sampling process, i.e., establishing the maximum allowable exposure time.

Surface monitoring methods provide an even greater challenge. In many cases, samples are collected from walls or surfaces that have been disinfected with an antimicrobial agent. There is the potential for antimicrobial action during the collection of the sample. This is frequently addressed by the addition of neutralizers to the media. The most commonly used neutralizers are Tween 80 (polysorbate 80) and/or lecithin. Another common neutralizer is Sodium Pyruvate, which is used to neutralize residual vaporized hydrogen peroxide. Another concern is residual antibiotic that may be present in facilities where antimicrobials are manufactured. This is also addressed by the addition of neutralizers or other chemicals to inactivate the antimicrobial agent, e.g., penicillinases, cephalosporinases. A more difficult issue to resolve is the recovery of organisms from the surfaces. Many cleanroom environments have high velocity airflow. During validation, one might wish to inoculate the surface with microorganisms. The issue is that the very dry environment in the cleanroom may kill the microorganisms before they can be recovered in the sampling method. This makes it difficult to show that the method recovers any organisms present.

Selection of Equipment

There are a wide variety of types of equipment available. They may be portable or fixed, i.e., permanently installed at a specific location(s). Depending upon the manufacturer and model of the equipment, the ability to clean or sterilize the equipment varies greatly. Selection of equipment involves reviewing the advantages and disadvantages of each type of equipment and selecting the system that will perform the testing required with the least risk and the most benefits.

The current trend is to install continuous particulate monitoring equipment. While this type of system is typically the least intrusive to the process, i.e., since it is permanently installed and no people are required to collect the samples it reduces the risk of contamination from sampling, there are several concerns when installing this type of system. Some of the considerations include: how to address deviations from the standard operating levels during operations that are known to generate particulates, e.g., cleaning; determining the maximum allowable distance from the sample collection site to the data collection site (computer and manifold); assessing whether delays be programmed into the system to allow for opening/closing doors; if delays are used determining what is an appropriate time period for the delays; and determining the number of sampling sites to use to obtain the most meaningful data and the least disruption of the environment.

Selection of Sampling Sites

In older environmental control programs, one typically performed grid analysis to determine where sampling sites should be located. In this type of approach, the area to be sampled is broken down into a series of boxes or grids of a specific size. Within this grid, one collects a surface and air sample. The samples are analyzed and the sample locations with the highest number of counts are selected for subsequent sampling activities.

More recently, companies have added philosophical analysis to add sample sites where the potential for contamination is higher, e.g., high traffic areas, areas where the risk of contamination is highest, areas where the product is subjected to the greatest risk.

Current regulatory expectations are that programs be established using a form of risk-based analysis. Several different risk approaches are available, e.g., failure mode and effect analysis, hazard analysis and critical control points, technical assessments, and so forth.

Additionally, the methods used and the specifics of testing should be documented in standard procedures or policies.

Establishing Levels/Limits

A variety of methods are available for establishing limits or levels. Appropriate values should be established to ensure that one can identify when the system is operating within a state of control, and when there is a potential or real drift from the expected control values.

The values selected should reflect control of the process rather than selecting arbitrary numbers. In some cases, the regulatory requirements for some areas have mandatory limits/levels established. This may necessitate setting a value for that reason alone.

Many statistical methods should not be used routinely, since they depend upon normally distributed data. Frequently, cleanroom data is not normally distributed. One method that is used to resolve this issue is to use the logarithmic conversion of the data. In most cases, the log transfer values are normally distributed. Another issue with some statistical methods is that when an environment is typically very clean, like Class 100/Grade A/ISO 5 areas, and a significant number of zero's are obtained it is potentially possible to obtain lower and lower statistical values for the limits/levels. In some cases, this may result in numbers that do not reflect a real state of control in the area.

Some companies have changed to using 'hit rates' or 'frequency analysis' to determine the state of control, e.g., if the percentage of samples resulting in growth is increasing the environment is deteriorating, while if it is decreasing the environment is improving. In these cases, one might also look at these percentages for the entire facility to determine the overall state of control.

Other methods are described in PDA Technical Report No. 13 (revised) (2001).

Data Collection Methods

Data may be collected by manually recording the results in laboratory notebooks or on worksheets. Automated systems, e.g., palm pilot-type devices, may also be used to collect the data electronically. Some sampling equipment also allows for paperless collection of data that may then be electronically transferred to a data management system.

Data Analysis and Management

A copious amount of data is generated in most environmental control programs. It is necessary to standardize the various methods to be used to analyze and interpret the

data. When one has a great deal of data, it needs to be organized and evaluated to be useful. It is also important to define what constitutes an adverse trend.

Looking through literature articles and regulatory guidance documents one will not find one generally accepted definition of an adverse trend. *The PDA Technical Report Number 13 (Revised) on Environmental Monitoring* provides some considerations when defining adverse trends. The *Aseptic Processing Guidance* indicates that it is not sufficient to define adverse trends as consecutive counts that exceed limits (FDA, 2004). If plotting the environmental monitoring results obtained, one can clearly identify plots where the values gradually increase as being a trend. Other results are not so easily interpreted. For example, when values go up and down, what does it take to say something is wrong? In aseptic processing Class 100/Grade A/ISO 5 areas many companies have established limits or levels of zero and one, where zero is acceptable and one is an excursion. There is no easy way to observe trends when using these values. Other methodologies, e.g., cumulative frequency analysis or determination of 'hit' rates, although not true trend analysis may be more appropriately used for data evaluation. When using this type of methodology, if the frequency of recovering counts increases, i.e., you obtain counts more often, this would be analogous to an adverse trend. Since the definition of an adverse trend is very subjective, it becomes necessary for each company to develop their own definitions and ensure that the definitions are clearly described in procedures or policies. Obtaining consensus on what defines an adverse trend is frequently difficult.

After one has established a definition for an adverse trend, one must determine the time period to be evaluated for short-term and long-term trends. From a microbiology laboratory perspective it is common to look at long-term data for a year. In some cases, the time period has been extended to two years to account for seasonal differences. In the last few years, some regulatory agency presentations at industry conferences provided examples of data where the time period considered for an adverse trend was three years. It appears that the length of time to be considered in long-term trend analysis is expanding and this can provide some challenges for the user. There is a copious amount of data that is collected on a daily basis for environmental monitoring. Maintaining this data, even electronically, can necessitate a significant amount of storage space. In the event that this data is stored on a company network, it frequently must be backed-up or copied to ensure data integrity and maintenance.

Due to the large amount of data that must be maintained and reviewed, many companies have purchased data storage and management systems. There are some off-the-shelf computer programs that may be used for this purpose. Additionally, some Laboratory Information Management Systems (LIMS) have modules available for the monitoring and trending of environmental data. While these programs provide a distinct advantage over the laboratory notebooks, and spreadsheet programs used in the past, over reliance on these systems to identify all trends and adverse findings is inappropriate. The ability of the system to detect trends is based upon the algorithms

and premises of the system. It is still necessary for microbiologists to look at the data obtained and evaluate whether additional testing or consideration is necessary. For many smaller pharmaceutical companies, e.g., generic manufacturers, and small divisions of larger pharmaceutical companies the cost of these programs may prohibit the use of the software.

In addition to the initial purchase of these software programs, the cost of validating the software can also be prohibitive. No matter how many different ways data is plotted, there is always another way to present the data. As a result, the number of report options available in these software programs increases to meet customer demands. Unfortunately, the more flexibility available in a software program correlates to an increased cost in validating the program. In addition to the sheer cost of validation, the time necessary to complete the validation may be prohibitive. For example, some small facilities may only have three or four microbiologists to perform all activities required. If one microbiologist is needed to work on validation for months, the work of the laboratory is significantly disrupted. Another concern is how the data will be managed during the time periods when new versions of software are being installed and updated.

It is possible with some software systems to set up a 'plant' or other database that is only used for validation testing. In these cases, it may require another computer have the 'test' software operating, while other copies continue to be used for daily operations. Although many automated software testing tools are available, for the most part they have not been incorporated into laboratory testing procedures. It is becoming necessary for pharmaceutical companies to learn from the examples of the automotive and electronics industries and better utilize failure mode analysis testing and other risk-based analysis tools to develop validation tests that provide the most benefit for the time taken in testing.

Identification/Characterization of Isolates

There are many interpretations of the level to which isolates must be identified when found in the environment. The sterilization process used may have an effect on the types of information required. For example, in a terminal sterilization process the main issue for environmental isolates is whether the number or type of organisms found are spore forming bacteria, and what is the heat resistance of these organisms. Since only bacilli (rods) form spores, a Gram stain may be used to determine whether the isolate collected is capable of forming spores. If spore forming organisms are found, heat screening studies may be required to determine the relative heat resistance of these organisms. For organisms that do not produce spores, no other characterization may be necessary.

In an aseptic process, the requirements for characterization/identification of isolates are more stringent. Depending upon the regulatory agency involved, characterization may only be required when levels/limits are exceeded. Other regulatory agencies have an expectation that routine identification be performed to gain an understanding of the contamination present in a facility and how this contamination is tracked through the facility. In other cases, there is an increasing interest in the routine use of nucleic acid identification methods for organisms present throughout the facility to learn about the potential routes of contamination, as well as clearly identifying the root cause of problems that may occur (FDA Aseptic, 2004).

Identifications to support investigations, troubleshooting and root cause analysis can be very valuable. In many cases, it may be necessary to use a genetic method to ensure that the organism found is actually related to a source of contamination. These methods are extremely important for analysis of sterility test positives and media fill positives.

It is important to note that all of the automated systems for identification have both advantages and disadvantages. Care should be taken to use the right system for the right task. Data should be generated to gain understanding of the accuracy, precision, reliability, robustness, and so forth for the system. These systems should be validated for use.

There are several issues common to these types of systems, e.g., environmental isolates may not respond in the same way as laboratory stock suspensions. As such, it may be difficult to obtain a correct identification with both forms of the organism. Many commercially available systems were developed based upon needs in the clinical arena and as such do not have libraries that are complete for environmental isolates; although this improved during the years these systems have been in use. Frequently nucleic acid or genetic methods have been considered the 'gold standard.' It is important to understand that most of these methods do not analyze the entire genome. As such, the section of the genome selected for evaluation may influence the identification provided. There are systems that evaluate the entire genome, but the cost of using these systems may not be warranted. Another common concern is the constantly changing genus and species names by organizations like *Bergey's Manual.* How the name changes are handled by the software and whether the software recognized the new organism name as being identical to the previous organism name should be understood.

Isolators

The need for performing environmental monitoring in isolator and barrier systems is a frequent subject of debate. On one hand, there are requirements for environmental monitoring; yet on the other side, one must be concerned with adding testing that is

more likely to contaminate the site versus providing useful information. Some systems for monitoring are easier to use with this type of technology, since they have remote sampling probes and are automated. The individuals designing sampling plans and procedures for these types of systems must analyze both the cost and benefits of the monitoring program.

Data Misapplications

One of the inherent problems in recent years is the concept that environmental monitoring data provides predictive data regarding the sterility assurance of the product. Unlike terminal sterilization processes, there are no mathematical equations that allow you to use the data generated from environmental monitoring in an aseptic process to calculate the product sterility assurance. This is important as the data from any given day does not provide a method to ensure the likelihood of sterility for future batches of product.

Another way in which environmental monitoring data is misapplied is use of this data to be a defacto sterility test. Numerous literature sources indicate that the sterility test methodology used in the compendia has limited value. For example, due to the small number of samples taken (i.e., not representative of the batch size), the limitations of the test conditions to recover all organisms present, and the sensitivity of the test method (e.g., sufficient growth must be present to be visible to the naked eye, i.e., growth of about 10^6 organisms/mL), the test really is only to detect gross contamination of the product. As more information became available regarding the limitations of the sterility test, the emphasis on environmental monitoring has increased to a point where many individuals look at the methodology as a second so-called sterility test method.

Many individuals tend to think that all of the microorganisms that are present in the environment have the ability to see the open containers like a search and destroy missile, and then do all kinds of maneuvers to get into the container. Yet there is no scientific data to support this view. The data generated in studies of the airflow patterns and smoke studies clearly indicate that the flow of air in an appropriately designed cleanroom environment make it highly unlikely, if not impossible, for this to occur. The airflow direction and velocity force any contaminants present down and away from the opening of the container. Additionally, if a very low level of contamination is present many times it is more likely to die off rather than thrive (also called quorum sensing) and grow, or to become viable, but not culturable.

When one has data generated that is outside of the established process control values, there is an expectation to take some action. When looking at environmental monitoring data, one should really be looking for trends. The methods used for collection of samples and reading of results are conducted manually and prone to

contamination during the sampling and testing methods. When an excursion or unexpected result occurs it is difficult to determine whether the fault is due to the sampling/testing method or an actual change in the environment. Does this mean that one should ignore the data generated; absolutely not. Rather one should use good science to determine what actions are appropriate for a single result that is exceeded. It is better to evaluate the trends that are occurring when evaluating the appropriateness of the environment.

Cost of Testing

Frequently one may hear a comment such as *"regulators are not interested in the cost of testing/compliance."* This comment is very distressing, since there are significant concerns worldwide regarding the cost of pharmaceutical products. Many times during a regulatory inspection or other type of audit someone will recommend that adding a sample site at this location may be useful. Many times, in order to resolve the audit or inspection quickly, we add the sample site. Although this seems like the least expensive way to resolve the issue, the actual cost of each sample and test is about $7–10. When one then adds the costs of maintaining this data in a database and summarizing the data for trend analysis and so forth, the real cost over the two or three years of data evaluation may double. In reality, the new sample location may provide little or no value to assessment of environmental control and rather just add to the standard cost of the product.

Another area where cost is an issue is the performance of genetic identification methods for isolates. These methods are very useful for troubleshooting, resolving issues with sterility test positives, media fill positives, and so forth. Unfortunately, the cost of these methods may or may not be prohibitive when analyzed against the benefit obtained from this level of identification. In many cases, less expensive methods can be used to rule out other potential sources of contamination.

Root Cause Analysis for Deviations

In the event that something unexpected occurs, e.g., an adverse trend, appropriate action should be taken to determine what the causative agent for the deviation is. Many times, opinions are used to determine the cause of the failure. This may be useful, but a systematic approach to analyzing the data and determining the root cause is useful. There are a significant number of quality problem solving tools available, e.g., Pareto Analysis, Fishbone Diagrams and so forth. These tools may also be used for environmental data.

One of the key concerns with this analysis is to determine whether there is an assignable cause for the failure, e.g., a dropped sample, incorrect test methodology,

and so forth. Should an assignable cause be identified, the test result is usually declared invalid, i.e., not a real sample failure. Many of the investigations and troubleshooting procedures used for environmental monitoring can be identified and a checklist or Standard Operating Procedure (SOP) can be designed to inform users on how to perform the investigation to determine the root cause of the problem. Frequently, unfortunately, the actual root cause cannot be identified and only hypotheses can be made relative to the cause.

When conducting investigations for sterility test positives or media fill failures, it is more difficult to invalidate the test results. It is the expectation of many regulatory inspectors that a nucleic acid method for identification of microorganisms is the only appropriate method for proving that the cause of the contamination is identified.

Performing Investigations

Investigations are required when deviations occur. This is specified in the GMPs for both the United States and the European Union (FDA CFR 211, Eudralex Volume 4). It is useful to identify the requirements for performing investigations in a standard operating procedure or policy document. This procedure should identify who is responsible for conducting the investigation, the methods to be used during the investigation, how the investigation should be documented, whether additional testing or data is required, how the data should be evaluated, rules for how product disposition is determined, who must approve the investigations, and how the investigation is closed.

In environmental monitoring, many of the actions taken for deviations are very consistent. This allows for a checklist or template to be created. This document may then be used to systematize the investigation process, allowing for complete and consistent evaluations to be made. Automated systems are available to track and manage the investigation process. Microbiologists should always be part of the investigation team for environmental monitoring issues.

Evaluating the Effectiveness of Corrective Actions

Any environmental monitoring program that is established should include evaluation of the effectiveness of corrective actions. One way that this occurs is through the use of trending reports. Another method used is to have a definite program in place to go back to each deviation on a periodic basis to determine whether the issues found are resolved.

Management Oversight

There is an increased expectation that senior management be involved in the resolution of problems in an environmental monitoring program. Some companies have either microbiology or sterility assurance functions that oversee the different programs established. These functions may meet on a periodic basis to discuss the status of the program, any deviations/investigations conducted, root cause analysis discussions, data trends, data reports, and corrective actions taken. Procedures should clearly describe how management is involved in these processes.

DESIGNING A CLEANROOM FOR THE 21ST CENTURY

While some companies are looking at isolator or barrier systems to meet their requirements of design for the future, other companies continue to use cleanrooms. In building a cleanroom environment today and trying to prepare for the future, one might want to consider cleanroom touch pads or computer terminals that allow for automated entry of data in the room. One may also want to consider installing sampling devices for both viable and non-viable microorganisms. For those procedures which involve manual data collection, palm pilot-type of data collection devices may be necessary that can directly download to the computer system, and allow for direct data transfer without other risks of contamination. The technology is also available for application of Process Analytical Technologies (PAT) and obtaining real time data for many of the chemistry and microbiology tests that must be performed.

CONCLUSIONS

Designing an environmental control program should be conducted by a multi-disciplinary team including both engineers and microbiologists. These individuals should create appropriate documentation for the system. This documentation should provide guidance on the philosophy and design considerations that were used in establishing the program within applicable regulatory documents. Lastly, and maybe most importantly, the program designed should be meaningful, manageable and defendable.

The remaining chapters in this book provide a more detailed explanation of the topics and issues described in this chapter.

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