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ESTABLISHING ONGOING MONITORING, SURVEILLANCE AND EVALUATION PROGRAMS

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INTRODUCTION

Once a system has been developed, appropriate procedures should be established to maintain the system in a production environment. This includes establishing procedures for routine and ongoing monitoring and surveillance, and evaluation of the data obtained. This chapter provides an overview of these types of systems.

COMPONENTS OF THESE SYSTEMS

The environmental monitoring data that is generated should be collected in a manner that is in conformance with current Good Manufacturing Practices (cGMPs). The personnel supervising the environmental monitoring program should be competent in the appropriate scientific discipline and have the training (including within the industry) and the authority required to make and implement change. Equipment that is used should be calibrated, systems should be appropriately validated and/or qualified, media should be properly prepared, and all operational procedures should be written and followed.

The established procedures should include appropriate controls to support their use. Cleaning of the facility and equipment, sanitization/disinfection agents and procedures, sample site selection processes and specification of the frequency of testing are key components to a good environmental monitoring program. Alert and

Action levels should be established and based on individual sample sites, but one may also choose to specify the maximum number of microbial data deviations permitted in one area/system for a sampling period. The establishment of appropriate Alert and/or Action levels and a system for monitoring implies that all of the data obtained are subject to continual review, and that Alert and Action level decisions are made by designated and authorized personnel qualified to make such decisions. To effectively execute microbiological surveillance support systems require several components including:

- Documented system in place for identifying microbial data deviations
- Feedback mechanism for verification of any action taken in response to data
- All data should be documented
- Trending and/or data analysis
- Senior management should be involved, as appropriate

CLEANING AND SANITIZATION/DISINFECTION

Implementation of cleaning and sanitization procedures is a critical component of overall facility control. Environmental monitoring data are used in routinely determining the ongoing effectiveness of these procedures. Care should be taken to ensure that the cleaning personnel understand the criticality of the cleaning procedures and know how to properly perform these tasks.

It is common for companies to have an internal auditor or supervisor periodically verify the cleaning procedures used, typically without the knowledge of the personnel performing the tasks.

SAMPLE SITE SELECTION

Suitable sample sites vary widely depending on the cleanroom design and manufacturing process. Careful evaluation of each process should be made in selecting sites. The primary purpose of sampling should be to provide meaningful, interpretable data that can help identify actual or potential contamination problems associated with specific procedures, equipment, materials, and processes. Following the validation and

qualification exercises, sites should be established for routine monitoring. Risk analysis is recommended for performing this type of analysis. Some of the factors to consider in selecting sites for routine surveillance are:

- Which sites can be identified where one would expect microbial contamination most likely to have an adverse effect on product quality?
- What sites would be most likely to demonstrate the heaviest microbial proliferation during actual production?
- What type of risk analysis procedure should be used to select the sites?
- What sites would represent the most inaccessible or difficult areas to clean, sanitize, or disinfect?
- What mechanisms are likely to disperse microbes in the environment?
- Would the act of sampling at a given site disturb the environment sufficiently to cause erroneous data to be collected or contaminate product?
- Should sampling only be performed at the end of the shift?

It may not always be practical to select a site at the most crucial identified location. One should consider whether crucial site monitoring would actually increase risk of product contamination.

Other considerations in establishing an appropriate site for sampling include:

- Facility design
- Line configurations
- Validation data
- Manufacturing process information
- Historical data
- Test methodology, etc.

Selection of sites that are appropriate may change over time. On a long term basis, a company should establish procedures to re-evaluate the appropriateness of sampling locations.

SAMPLING FREQUENCY

Frequency of monitoring requirements varies widely in the industry depending on several factors including, for example:

- Type of manufacturing process
- Product
- Facility/process design
- Human intervention required
- Use of subsequent terminal sterilization
- Historical profiles of the microbiological environmental data

There is not one single sampling scheme that is appropriate for all environments.

Changes in sampling frequency, whether temporary or permanent, may be required based on changes in practices, compendial requirements, development of significant microbiological trends, and acquisition of new equipment, nearby construction of rooms or utilities, and so forth.

Monitoring frequencies should be selected that can identify potential system deficiencies. The test frequency per site may be less frequent than the system or area frequency (e.g., one may choose to rotate sample sites).

Prior to implementing any reduction in frequency, a summary of historical data, along with current and proposed sampling frequencies, should be reviewed and approved by the appropriate Quality Assurance (QA) personnel. After preparing these summaries, data should be reviewed periodically to determine if the reduced sampling frequency is still appropriate.

ALERT AND ACTION LEVELS

Most regulatory agencies require environmental monitoring programs have established Action levels based on the applicable guidelines and the review of historical data. Alert levels are also recommended. Some companies also choose to set levels for individual cleanrooms or sample sites. Typically, the Action levels will be driven by the regulatory or industry guidelines. The Alert levels will be driven by historical analysis of the environmental monitoring data. The application of Alert

and/or Action levels should be written and employed in a consistent, non-arbitrary manner. To create consistency in treatment of Alert and/or Action levels, logical investigatory and/or corrective action steps should be pre-specified. Records should show that the microbial data deviation was recognized and that appropriate follow-up occurred.

Once Alert and Action levels have been established, they should be periodically reviewed, as part of routine trend analysis. They may be revised to reflect improvements, advances in technology, changes in use patterns, or other changes. A variety of methods are used to establish these values.

DATA MANAGEMENT

Several different activities are part of data management, data collection, analysis of data, approaches used to analyze data, and interpretation of data. The routine review and analysis of environmental monitoring data is essential to aid in the interpretation of process stability and assess overall control performance. Management must be kept abreast of trends and the subsequent state of operations within their facilities.

Based on the large number of samples tested by a given facility, a computer-based data tracking system is recommended. Prior to implementation, all database applications used should be validated/qualified for specific software applications.

DATA COLLECTION

Routine data must be pooled into a designated database or spreadsheet in a consistent record format. The record format should include:

- Monitoring date
- Specific sampling locations
- Sampling methods
- Colony Forming Units (cfu) or number of organisms
- Non-viable count results
- Identification performed

- Product lot information
- Current Action/Alert level

The data tables can be completed using manual data entry, an image scanner system, or electronic entry into handheld devices. Data integrity must be verified prior to analysis.

ANALYSIS OF DATA

Environmental monitoring trends are often difficult to obtain and recognize, due to the low number of Colony Forming Unit (cfu) results usually obtained. Histograms, defined as pictorial graphs characterized by a number of data points that fall within a common frequency, are one valuable tool. Different room classifications with definite requirements will produce different histograms. Each area (or area type) and accompanying data set must be viewed as distinct. A mathematical model should be applied not only with the objective in mind, but also the type of data to be analyzed.

Grade A (ISO 5) areas where typical Action levels for samples may be one (1) microorganism, can be hard to trend. In these types of circumstances, rather than a pure trend of data one may calculate a hit rate, i.e., how often do you get a count divided by the number of samples taken. In this example, as the hit rate increases one would assume an adverse trend. As the hit rate decreases the environment is 'cleaner'.

APPROACH TO DATA MANAGEMENT

When data is being analyzed, it is important to understand how the assessment will be conducted. For example, a generalized method that may be used for data to assess the environmental control is:

- Determine objective of analysis (e.g., analysis of site location data, examination of a microbial data deviation, assessing the appropriateness of an established Action level, management update, and so forth).
- Specify the data set to be analyzed, e.g., one week, one month, only data from a specific site.
- Apply data plots, such as histograms or pictorial plots, to access the basic data and to determine the nature of the distribution, if any. The data plots can also be used to locate peculiarities such as outliers or patterns.

- Observe the distribution and proceed with the appropriate mathematical model that best fits the overall objective. If data conform to a normal distribution, a parametric mathematical model may be applied. If the data is not consistent with a normal distribution, then a non-parametric approach may be applicable.

- In this example, an Action level at the 99th percentile is employed. Consistent with the Action level at the 99th percentile are the following mathematical models (PDA, 2001). Models can only be applied if the data's character assumes a definite distribution.

    - Action level estimate for a data set reflecting an exponential or non normal distribution = 4.6 × (mean cfu)

    - Action level estimate for a data set reflecting a normal distribution = 2.33SD + (mean cfu)

    Note: When the Action Level is determined at the 99th percentile, an occasional excursion is expected due to the model applied. SD = Standard Deviation.

- Regardless of the statistical model chosen, the analytical method must be consistent with the data and documented in the data summary along with results.

INTERPRETATION OF DATA

All data generated should be summarized and evaluated to determine whether the environmental monitoring process is in a state of control.

IDENTIFICATION/CHARACTERIZATION OF ISOLATES

Characterizing microorganisms recovered from environmental and personnel monitoring is an important part of surveillance programs. The characterization system selected by the laboratory should be defined in writing, including the frequency of characterization and the standard procedures for the methods. Identification systems that are available have differing strengths and weaknesses. Procedures should carefully describe how the final identification is made when more than one identification system is used (PDA, 2001).

Initially, many isolates may be characterized to establish baseline data of the microorganisms found in the area.

Certain barriers apply to the characterization of environmental isolates. The microorganisms recovered from production environments may be highly stressed due to physical factors such as limited nutrients, contact with chemicals or thermal stress. It may be difficult to obtain genus/species matches in identification system databases. The databases for commercial test kits and identification systems were designed originally for clinical isolates and may be incomplete with regard to industrial isolates; this may lead to misidentification of species or unidentifiable isolates. This area is continuing to be developed and enhanced (PDA, 2001).

It should be noted that for aseptic processes, Regulatory inspectors have placed a strong emphasis on the use of nucleic acid based identification systems, especially for troubleshooting, root cause analysis, sterility test positives and media fill positives.

INVESTIGATIONS AND CORRECTIVE ACTIONS

When microbial data deviations occur, there can be a drift from the validated baseline. An investigation is needed to determine what happened and what needs to be done. Records should show that the excursions were recognized and appropriate follow-up occurred.

The overall purpose of the investigative action is to establish, to the greatest degree possible, a cause–effect relationship between the observed level of environmental quality and causes for the excursions (i.e., sources of contamination).

To create consistency in the treatment of microbial data deviations, investigative and/or corrective action, steps should be pre-specified in a written plan. A progression of investigative/corrective actions or responses may be used in which sequential or multiple excursions require greater consideration, than single or widely separate excursions. Likewise, deviations which occur in areas that are critical to the manufacturing process may require a more rigorous investigation and corrective action than those which occur in areas that are judged less critical to the integrity of the manufacturing process.

DOCUMENTATION METHODS

A large amount of data must be collected for each sample site to ensure that the data can be used in subsequent evaluations. Written procedures should identify the data requirements, as well as what must be kept.

ENVIRONMENTAL MONITORING FOR TERMINAL STERILIZATION PROCESSES

An environmental control program designed for a terminal sterilization process should be concerned with microbial flora that contributes to the spore bioburden of the product prior to sterilization. This includes testing of high purity water, distilled water, sterilizer cooling water, treated water and city water. Air, surfaces, and microbial levels of containers and closures are also routinely monitored. While control of the environment in which the products are prepared is important, the most critical aspect of the program is the spore bioburden of the filled product to be sterilized. Appropriate controls for the manufacturing process ensures that the spore (heat resistant) bioburden levels present in the product sterilization cycle do not exceed the validated capabilities of the process and that the desired sterility assurance levels are achieved (PDA, 2001).

ENVIRONMENTAL MONITORING FOR ASEPTIC PROCESSES

The monitoring program for aseptic processes is specifically designed to determine the number and type of microorganisms associated with direct assembly, or preparation of product, prior to sealing of the filled containers. The number of sample sites and frequency of monitoring are generally greater than monitored for established terminal sterilization processes. Air, water, personnel, compressed gases, floors, walls, machinery, and other surfaces within the filling room are routinely monitored. Microbial levels are also routinely monitored on containers and closures. Adequate environmental control is an integral part of the aseptic manufacturing process.

ENVIRONMENTAL MONITORING AND ISOLATION TECHNOLOGY

The environmental control program for aseptic filling isolator systems may be similar to that used for a conventional aseptic filling operation with the exception of surface and personnel monitoring. After sufficient data is collected, routine surface and air monitoring may not be warranted if a validated sanitization cycle exists for the interior surfaces of the isolator. However, particulate air sampling would be performed routinely. Surface monitoring may be used during initial validation runs to support the effectiveness of the sanitization cycle and maintenance of clean isolator surfaces between sanitization cycles. If surface monitoring is performed it should be done after the completion of filling so as not to introduce any extraneous contamination or residual growth media during the filling operation. Monitoring of personnel is not required for isolator systems; but monitoring of isolator gloves/half-suit is required.

WATER MONITORING

Water is the most widely used substance, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbial quality of water is of great importance in the parenteral manufacturing facility since it may be used for formulating product, as well as for various washing and rinsing processes. Once a water system is validated to be in a state of control, appropriate samples should be taken from the holding and distribution system to assess the microbiological quality for its intended use. In addition to requirements for pharmaceutical manufacturing, there are also requirements that must be met for drinking water in most countries.

The time elapsing between collection of water samples and examination typically should not exceed 24 hours. Each site should have validation data to support the time limitations imposed for collection and testing of samples (PDA, 2001).

MONITORING OF COMPRESSED GASES

Compressed air or other gas that is used, especially in an aseptic environment, should be tested as part of the normal room air on a frequency that would assure that the gas does not adversely effect the environment. Testing may be performed at a lower frequency than routine testing for monitoring the environment.

Nitrogen, which is heavier than air, is used as a blanket over some product formulations and in some tunnels. Argon, lighter than air, may also be used. However, the weight difference of the gas being sampled must be taken into consideration. The flow device used will have to be reset or designed to account for any differences, or there may be less or more gas in the sample than is recorded on the flow device. Accurate sampling of gases requires that one considers many parameters including:

- Elevation, i.e., any gas or air expelled into the environment should be at a level similar to that of the room.

- The typical aseptic manufacturing environment incorporates either a validated 0.45 or 0.2 μm filter. Testing may be performed as a confirmation of the filter's acceptability, as a test of the filter's completeness and not a test of the compressed air/gas system itself. Some operations may not incorporate a filter at point of use. A pre-filter may be installed in the system to reduce the bioburden to the point of use filter that will extend its life, and reduce the possibility of higher contamination reaching the area.

- The sterilization of components prior to use in the test instrument is critical.

- All compressed air connections, which do not affect the air to the workspace, should be monitored with less frequency; however, any connection which introduces air to the environment should be monitored on a frequency so as to assure the conditions of the aseptic environment.

- Precautionary measures should be taken when sampling gases which may have an explosive nature.

- A medium used for evaluation and incubation and rendering evaluations should follow the standard practice as for routine monitoring sites (PDA, 2001).

AIR MONITORING

A comprehensive environmental monitoring program should include routine monitoring of both viable and non-viable airborne particulates. Viable particulates are generally of significant concern in sterile product manufacturing environments; however, non-viable particulates should also be monitored as another source of potential product contamination. Current techniques for monitoring viable particulates in air are limited by: the equipment available; the time necessary to demonstrate the presence of microorganisms in the sample of air taken; the inability to re-sample the environment in a timely fashion when results warrant; and difficulties in continuously monitoring the environment due to considerations, such as drying out of the recovery media. With the advancement of rapid microbiological methods, these concerns may be minimized.

Non-Viable Particulate Monitoring

Monitoring of non-viable airborne particulates is a necessary component of an environmental monitoring program. Such monitoring demonstrates control of potential contaminants in the environment to which the product, during the manufacturing process, is exposed. Classification of production areas is generally made based upon the level of non-viable particulates in the air. Classified areas must continually meet these established particulate levels.

Viable Monitoring

Microorganisms present in the air are generally associated with solid or liquid particles. These particles may consist of a single unattached cell or, more commonly, as clumps of organisms. Organisms may adhere to a dust particle or other 'raft', or, if unattached, exist as a free-floating particle suspended in the air. These particles may

remain suspended in the air for extended periods of time due to the local air currents, but vertical unidirectional airflow, as well as gravity, will move them towards the floor or the nearest return air grill. (This assumes low-mounted returns, which may not always be the case. Fermentation areas may use high-mounted returns.)

SURFACE MONITORING

In addition to conducting viable air monitoring to determine the microbial bioburden surrounding the manufacturing operations, surface monitoring is conducted to determine the microbial bioburden of surfaces within the manufacturing area, as well as on equipment and product contact surfaces.

PERSONNEL MONITORING

Personnel introduce contamination in an aseptic environment, due to the microorganisms and non-living particulates present. It is essential that all employees entering an aseptic environment be carefully selected and trained. Training should include personal hygiene, an introduction to microbiology, aseptic techniques, and microbiological gowning certification. After an individual has been trained and certified, routine microbiological monitoring of garments and finger impressions should be completed to assess the ongoing practice of aseptic technique. All training and certification activities should be documented and kept as part of the employee file.

MONITORING PRODUCT OR COMPONENT BIOBURDEN

Bioburden testing is performed on non-sterile product to determine its microbial load. The intended use of the product will dictate the allowable acceptance levels and the exclusion of objectionable microorganisms at the time of formulation. Listed below are some factors that may impact product or component bioburden:

- Raw material source
- Water
- Components
- Manufacturing environment

- Processing of the formulation product
- Equipment
- Antimicrobial activity
- Water activity

For many terminally sterilized products, bioburden counts alone do not provide sufficient information. It may be necessary to assess the thermoresistance or D-value of the bioburden. Total bioburden counts that are within limits may cause a significant problem if the bioburden present exceeds the thermoresistance anticipated for the sterilization model.

D-values can be determined using sophisticated equipment (thermoresistometer) with square wave heating, and heat-up and cooling times less than or equal to 10 seconds. For routine screening of bioburden, a heat shock or boiling water test is used to rule out the presence of organisms exceeding a predetermined D-value.

PARAMETRIC RELEASE AND BIOBURDEN

Parametric release is a term used to describe sterilization processes that are so tightly controlled and understood that it is possible to ensure sterility of the product when the parameters are met, even without performing a sterility test. The allowance of pharmaceutical manufacturers to use parametric release under the approval of FDA in 1985 increased the importance of bioburden testing, characterization, and resistance of recovered microorganisms. *FDA Compliance Policy Guide* (7132a.13), issued in 1987, details the criteria that must be met for Parametric Release.

Major emphasis is placed on the thermal resistance of recovered spore forming microorganisms. Recovered spore formers with greater resistance than the indicator organism used in the cycle validation, would render the batch to be deemed non sterile.

IN-PROCESS TESTING

In-process environmental monitoring samples are taken to evaluate various parameters, including the ability of the equipment to perform within specified environmental quality standards; the operator's ability to maintain area cleanliness during process operations; and the effectiveness of cleaning for the facility and its equipment. This monitoring is typically performed in production areas, and during

operations, where product is exposed to environmental or operator contamination; however, it is not always included for closed systems, as the results may not have a correlation to product impact. Process-related monitoring may include surface and air sites near aseptic connections or product transfer steps. The manufacturing operations monitored may occur in an open room, under laminar flow, or within a 'closed' system. Sites should be chosen to demonstrate process integrity in both 'open' and 'closed' processes. Sample sites and levels should additionally be chosen to provide meaningful data about a given operation. As an example, non-viable particle counts taken during loading of powdered media into a vessel in a Class 100,000/ISO 8/Grade D area may not provide data that is indicative of process quality. Non-viable particle counts taken during aseptic processing operations (excluding powders) in Class 100/ISO 5/Grade A, areas may provide more valuable information about process control.

The subsequent purification/bioburden reduction steps in a process may also impact the degree to which in-processing testing is warranted. Test frequencies for batch-related, in-process monitoring may differ from those for routine area monitoring. In many cases environmental monitoring, performed in conjunction with batch production activities, may fulfill the requirements for routine area monitoring.

Surface and viable air samples that select for the host organism may be appropriate in a fermentation/recovery process area. This data may help to demonstrate process integrity and/or cleaning effectiveness during a product changeover procedure.

ENVIRONMENTAL MONITORING DURING ROUTINE STERILITY TESTING

Sterility testing facilities should be designed and operated in an equivalent manner to aseptic processing areas. Environmental monitoring should be conducted in an active mode during each shift, with Alert and Action levels set that are comparable to those used in aseptic process areas in the manufacturing plant. Monitoring should be conducted to demonstrate continuous microbial contamination control, consistent technician performance and to obtain information concerning the possible source of the microorganisms associated with sterility failures.

REFERENCES

PDA (September/October, 2001) Technical Report B Revised–Fundamentals of an Environmental Monitoring Program, *PDA J. Sci and Technol.* 55: 5.