

# Auditing Environmental Monitoring System

## Goals

**When you have completed this unit, you should be able to:**

- Perform an Environmental Monitoring Audit.
- Use a range of tools and information, including the contents of this unit and the Intranet, to support an Environmental Monitoring Audit.
- Apply worldwide regulatory agency requirements to Environmental Monitoring
- Recognize compliance or non-compliance of regulations regarding Environmental Monitoring requirements.

## Definitions

***Air changes:*** The frequency (minutes, hours, etc) with which the air in a controlled environment (classified area) is replaced. The air can be recirculated partially or totally replaced.

***Air classifications:*** Classification of processing rooms or areas based on the allowed number of particles per cubic foot of air (USA) e.g. class 100, or particles per cubic meter (EU) depending on level of activity in the processing room. The EU refers to these air classifications as Grades A through D, with A being the cleanest during normal activity.

***Air Lock:*** A small room with interlocked doors, constructed to maintain air pressure control between adjoined rooms (generally with different air cleanliness standards). The intent of the air lock is to preclude ingress of particulate matter and microorganism contamination from a lesser controlled area.

***Air samplers:*** A calibrated piece of equipment that samples air by impacting a calculated amount of air onto a solid or semi-solid microbial growth media over a specified period of time. These samplers are used to determine the viable (microbiological) content of the air in the processing room. Some accepted samplers are Slit-To-Agar (STA) samplers, Centrifugal Samplers (CS), and Sieve Microbial Atrium (SMA) samplers.

***Action levels:*** Established microbial or particle levels that, when exceeded, should trigger an appropriate investigation and corrective action based on the investigation.

***Alert levels:*** Established static and operational microbial or particulate levels giving early warning of potential drift from normal operating conditions which are not necessarily grounds for definitive corrective action but which require follow-up investigation.

***Classified area:*** This is an area that is qualified and monitored against a defined particulate level (e.g. ISO 5-8 and EU Grade A-D).

***Clean Area:*** An area with defined environmental control of particulate and microbial contamination constructed and used in such a way as to reduce the introduction, generation, and retention of contamination within the area.

## **Auditing Environmental Monitoring System**

### **Establishing an environmental monitoring program**

It is necessary to establish what to look for when designing a monitoring program, e.g common aerobic bacteria, moulds and/or anaerobic bacteria. Equally important is to set the objectives of the environmental monitoring program. Normally the program

should provide supporting data to demonstrate the adequacy/performance of the contamination/environmental control measures taken. Monitoring may include:

- People
  - Exit monitoring
  - Aseptic practice
  
- Plant
  - Airborne contamination
  - Surfaces
  
- Materials
  - Components
  - Pre-filtration/pre-sterilization bioburden

Techniques such as Hazard Analysis and Critical Control Point (HACCP) can be used in order to focus a monitoring program on where the product is at greatest risk of contamination. Product as well as process characteristics should be taken into account.

Product characteristics

- Terminal sterilization versus Aseptic Processing
- Microbiological vulnerability

Process characteristics

- Process design
- Product flow
- Personnel flow and numbers
- Working patterns (shifts?)
- Plant occupancy and levels of activity
- Points in process where the product is at greatest risk

Generally a microbiological monitoring program is constituted by two parts. Firstly a general monitoring scheme that aims to demonstrate the effectiveness of maintenance, housekeeping, operator discipline and compliance with established standards. Secondly a batch/process specific scheme that aims to take account of the specific characteristics of individual processes and to provide batch specific information on the potential for product contamination and thus be used in the batch disposition process as well as also demonstrating compliance with established standards.

For the general monitoring schemes (effectiveness of housekeeping, maintenance and operator discipline) sampling locations should be chosen which can adequately provide data on such parameters. The locations should give good coverage of the whole clean room and associated areas (changing rooms, air locks, transfer hatches and preparation areas). They should be chosen in order to include “worst case” locations such as high traffic areas, low airflow areas and sinks. Locations should be realistic in order to mirror the overall condition of the manufacturing environment.

For the batch/process specific monitoring schemes sampling locations should be chosen to reveal potential problems with process and/or product integrity. They should thus reflect the process flow pattern and monitoring should follow the product flow through the manufacturing area. In particular points in the process where the product and

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Utilities that should be monitored include the HVAC system, the water system, and compressed gases that may come in contact with either the exposed product itself or the air that the product is exposed to.

Compressed gases should be tested for viable and non-viable particulates.

The Water for Injection (WFI) system should be monitored on a routine basis. Tests that should be performed include microbial quality and endotoxin tests as well as USP

chemical tests. The reason for testing this water is that it may be used as a solvent for preparation of parenteral solutions and also for final product formulation.

Potable water, purified water, the feed water for WFI and component rinse water should also be tested on a regular basis. Results of the tests should be analyzed for trends that might be developing.

### **Types of Air and Surface Monitoring**

Within an environmental monitoring program there are various types of testing performed. The testing can be divided into two major categories. These categories are testing for

1. Non-viable contaminants and
2. Viable contaminants.

#### **Non-viable contaminants**

This category tests for non-living particulates or particles that contaminate a sterile product. This would include dust particles, dirt, rust, tiny metal shavings, lint from a garment, human particulates, and other sub-visible particles that can still contaminate a sterile product if they are present in the product.

Factors that are tested for this category of contaminant include:

- Air in the processing area and support area
- Compressed gases

Expectations of world wide regulatory agencies are that the most critical processing areas where sterile product or components are exposed to the air during processing should be monitored for non-viable particulates. The particle load, from an air sample taken under normal processing activity (i.e. dynamic conditions), should be evaluated in accordance with EN ISO 14644-1, EU GMP Annex 1 and FDA requirements as appropriate.

The purpose of particulate monitoring is to demonstrate that the particle load of the air just before it encounters the working plane of concern where there may be product or sterile material/container/closure/equipment surface exposure. It is not to sample, count, and size particles associated with equipment operation.

Non-viable air sampling should routinely be conducted during aseptic processing. Placement of the sampling device in grade A areas should generally be within one foot and directly upstream of the working plane where exposure of critical items or materials take place. The sampling device should be properly oriented to sample the HEPA filtered air just before it reaches the areas where critical items or materials are exposed.

Placement of the sampling devices in other areas of the processing suite is less prescriptive since these areas are usually subject to turbulent flow. The frequency of the air testing should be every time the aseptic processing area is in use. Support areas may be tested less frequently, such as component preparation areas in controlled areas. All testing intervals should be defined within an approved procedure.

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- Chlorine compounds (e.g. Sodium Hypochlorite) have broad-spectrum activity, are sporicidal and are not affected by hard water nor natural/manmade materials and leave very little residue. However, they are inactivated by organics, lose activity on prolonged storage and exposure to UV-light, are corrosive and not good cleaning agents.
- Glutaraldehydes (e.g. Tegodor) are broad spectrum and non-staining/corrosive. However, they are unstable in solution, irritating to skin and inactivated by organics.

Routine sanitization should include all critical areas, walls, ceilings and floors. Particular consideration should be given to change rooms, transfer hatches and other areas frequently used. Rotation of sanitization agents used may be done in order to prevent development of resistant microbiological flora. In any case agents should be chosen in order to achieve a wider spectrum of antibacterial effect.

### **Summary**

All of the factors mentioned above need to be aligned and integrated to produce a clean environment for the processing of sterile drug products. If any one of them is not within limits or not working properly, it can affect the whole processing environment and jeopardize the sterility, integrity, potency, and quality of the final drug product. The goal of the environmental monitoring system is to control contamination through the rigorous monitoring of all of these factors and prevent loss of control through early detection.

## **Key Parameters for Auditing an Environmental Monitoring System**

### **Prior to the audit**

- Determine what type of environmental monitoring will be required for the products manufactured at the site.
- Review previous inspections and audit.
- Review listed reference materials found in this unit to familiarize yourself with worldwide regulatory expectations.

### **During the audit**

- Inspect the facility utilities.
  - Compressed gases, water systems, steam, and HVAC systems.
    - Determine if all utility systems with product contact and/or aseptic processing components have been qualified.
    - Determine what routine testing of these systems is conducted and how often.
    - Determine what the microbial action and alert levels are for compressed gases, HVAC systems, water, and steam.
    - Determine what the particulate action and alert levels are for compressed gases and HVAC.
    - Review action and alert limits to determine if they are appropriate.
    - Determine if there is a site procedure listing what actions need to be taken if any of these systems exceed these limits.
    - Determine if these procedures for “over limits” are followed.