

**Auditing Environmental Monitoring System**

<b>Title: Auditing Environmental Monitoring System</b>					
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**Audit Training Manual: 013**

**Auditing Environmental  
Monitoring System**

## Auditing Environmental Monitoring System

**Contact plates:** Usually a plastic plate that has a raised surface composed of microbiological solid media. The media is then pressed or rolled upon a surface, transferring the content of the surface to the media. RODACs (Replicate Organism Direct Agar Contact) plates are one example.

**Continuous monitoring:** Ongoing sampling of environmental conditions throughout the period of operations, ensuring that update of data occurs constantly.

**Controlled environment:** Any area in an aseptic process system for which airborne particulate and microorganism levels are controlled to specific levels that are appropriate to the activities conducted within that environment.

**Critical surfaces:** Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout the process.

**Dynamic / “in-operation” testing:** Testing performed during processing operations or within an active shift (as applicable) with personnel present to confirm that the environment remains under control during these conditions.

**Excursion:** A testing result that deviates from normal expectations defined by the firm.

**Incident rates:** The rate or frequency at which contamination is observed in an environment. Typically expressed as a percentage of samples in which contamination is observed per unit time.

**Laminar flow:** An airflow moving in a single direction and in parallel layers at a constant velocity from the beginning to the end of a straight-line vector. However, true laminarity is not achievable in clean room applications. “Unidirectional flow” is the more accurate description for clean room applications and is defined as; an airflow moving in a single direction, in a robust and uniform manner and at sufficient speed to reproducibly sweep particles away from the critical processing or testing areas.

**Particulate monitoring:** Testing of the processing air for various sizes of viable and non-viable particles. Continuous monitoring is required in grade A and recommended for grade B by EU. FDA is less prescriptive and only state that such monitoring be frequent.

**Sanitization Schedules:** Schedules established by the firm to sanitize the cleanroom facility surfaces, e.g. walls, ceilings, floors. Schedules may vary depending on the use and condition of the room. The schedule is to be part of an approved procedure for housekeeping and cleaning of the aseptic area.

**Settling or settle plates:** Usually petri dishes containing a microbial growth media, like agar, which are distributed throughout an area, media side up, to measure the viable content of the air over a specified period of time. This is a passive system that catches microorganisms as they fall onto plates.

**Static / “at rest” testing:** Testing performed with equipment installed but no personnel present to ensure that the facility environment continues to perform as designed and is compliant during normal operation.

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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 components are exposed to the environment should be taken into account. The microbiological cleanliness of the gloves of operators intruding critical zones should also be monitored. Sampling should generally include: air sampling (active and passive), hard surface sampling (at or adjacent to critical areas), operators, liquid sampling (e.g. bioburden).

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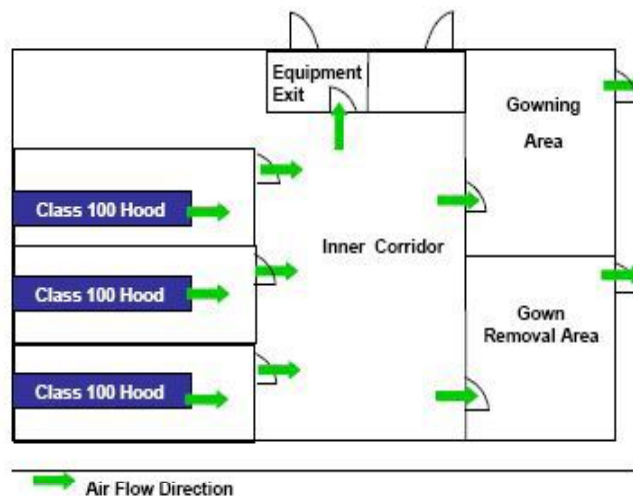
passive reading of the environment. It cannot be used to justify bad practice with supposedly good data. In such case all that is indicated is that the environmental programme is also poor.

### Temperature and Relative Humidity Monitoring

Temperature and relative humidity should be controlled and monitored as appropriate. For the processing area, both of these factors should be connected to an alarm system. If the temperature and humidity are elevated, personnel may begin to shed increasing numbers of skin cells and sweat causing more potential contamination. An approved SOP or procedure should be in place explaining what actions should be taken if a temperature or humidity excursion occurs.

### Pressure Differentials

Appropriate pressure differentials from room to room and area-to-area is necessary to prevent contamination of the drug product. A positive pressure differential between the most critical area and the next critical area should be maintained. Pressure differentials should be monitored and alarmed continuously. A typical pressure and airflow for the area should look something like that shown below:



The flow of air should be out of the critical areas into the adjacent areas, unless the opposite is required due to safety or cross-contamination reasons. How to handle ventilation failures should be described in SOPs.

The critical areas, where product is exposed, should also be the cleanest areas, with the fewest numbers of particles and microbes.

### Utilities

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

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extent of identification performed in other areas should be based on a written program that seeks to adequately characterize the environment to determine if there are any trends or shifts in isolates observed and whether any atypical isolates are present such as fungal organisms, gram-negative bacteria or spore forming gram-positive bacteria.

To determine if microorganisms are present, there are a number of methods in use to determine if microorganisms are present. Some of the most common are:

### ***Surfaces***

- Contact plate method
- Swab method

### ***Air Testing***

- Settling Plate method
- Impaction/Impinger methods

### **Monitoring of Surfaces**

Ideally, surface monitoring should be performed to represent the area while in production mode. Considerations should include the type and level of activity that represent actual filling processes. Some surfaces may be tested during operations or before operations begin. The frequency should be every time the aseptic processing area is used. Critical surfaces within the filling area and personnel testing should be included as part of surface testing. However, surfaces in critical zones should only be monitored after the conclusion of operations due to the risk of bringing microbiological culture medium into the environment where critical activities are taking place. Monitoring of surfaces in surrounding areas during operations also poses the risk of leaving residue of microbiological culture medium on the sampled surface and so should only be done where absolutely necessary and with strict controls

Additional surface testing should also be performed on random items that personnel frequently come in contact in an effort to identify potential contamination sources. Examples are curtains surrounding the Class 100/grade A area, door plates, phones and tools. The next paragraphs briefly describe methods used for surface testing.

### ***Contact plate method:***

The contact plate, or RODAC (Replicate Organism Direct Agar Contact) plate, consists of a solid general nutrient agar media, approximately 25cm which can withstand being pressed onto a surface or object. The sample is taken by gently rolling the raised surface of the agar plate onto a flat or slightly curved surface for a defined time interval. After the test is conducted, the area tested should be wiped using a lint-free wipe soaked in disinfectant (isopropyl alcohol, IPA, is most commonly used) to remove residual agar according to the site's SOP. The plate is covered and incubated at an appropriate temperature. The presence and number of microorganisms is detected by the appearance of colonies on the surface of the plate.



### **USE:**

- Personnel gloves and gowns
- Filling room surfaces
- Determining the effectiveness of cleaning and sanitization procedures

### ***Swab method:***

The swab method is used to obtain a sample from small or irregularly shaped objects or surfaces. Samples are collected by swabbing the surface or object with a moistened sterile swab containing sterile diluent to assure uniform coverage of the sampled area. The swab is then transferred into a container with growth medium. The swab and container are then incubated



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contamination.

As mentioned before, personnel need to be routinely tested in conjunction with activities performed in the aseptic processing area. The EC Guide to Good Manufacturing Practice – Revision to Annex 1 states that surfaces and personnel should be monitored after critical operations. Personnel testing, usually using RODAC plates is performed on glove and gown sites. Monitoring should be performed as soon as possible upon completion of critical tasks. Firms are expected to establish limits based on recommendations from worldwide regulatory documents as well as data collected from monitoring.

### Sanitization

Sanitization of the processing area should be assessed. Suitability, efficacy, and limitations of the sanitization agents must be determined based on their ability to inhibit or remove microbial contaminants commonly found in the processing areas and adjacent areas. In the choice of sanitization agent the spectrum of activity, sporicidal effect, inactivation by organics/materials/hard water and residues/corrosion, safety, contact time required, stability and cost must be considered. The firm should have an approved sanitization program with detailed procedures.

Based on different chemical characteristics and mode of action sanitization agents can be grouped. The norm mechanism is destruction bacterial proteins by oxidation.

- Alcohols (e.g. IPA, Ethyl Alcohol) are normally used in 70% concentration and have broad-spectrum activity, rapid action, leave minimum residue, are generally not affected by organics or materials and provide some cleaning effect. However, they are flammable, costly and not sporicidal.
- Quaternary Ammonium Chloride Compounds (e.g. Cetrimide, Benzalkonium Chloride) are very active against gram-positive organisms, stable, soluble, compatible with detergents, fungicidal and are inexpensive. However, they are not sporicidal and may be affected by hard water and organic material.
- Phenolic compounds (e.g. Chloroxylenol) are generally fungicidal, broad spectrum biocidal and very soluble. However, they are not sporicidal and hard water, some organic materials and natural soap may reduce their effectiveness. Additionally they are no good cleaning agents and may swell rubber and some plastics.
- Iodophors are quick in microbial kill, very active against gram-positive bacteria and generally less skin irritating than other sanitization agents. However, they are not good cleaning agents, may stain plastics, inactivated when exposed to UV-light and may be inactivated by organic material.
- 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 inactivate by organics, loose activity on prolonged storage and exposure to UV-light, are corrosive and not good cleaning agents.
- Gluteraldehydes (e.g. Tegodor) are broad spectrum and non-staining/corrosive. However, they are unstable in solution, irritating to skin and inactivated by organics.

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- within a defined space.
  - If air velocity is monitored, review the data. Compare readings with validated conditions.
  - Ensure that air pressure differentials within controlled areas are continuously monitored and alarmed to indicate when the air pressure is out-of-range.
  - Determine what the pressure differential alarm delay specifications are and how they were established.
  - Determine what procedures are followed in response to these types of alarms. Ensure appropriate and timely actions are taken.
  - Ensure that the minimum pressure differential between rooms of different classifications is .05" water or 10-15 pascals.
  - Ensure that the direction of air flow is correct.
  - Determine if the site has an approved procedure that defines the maximum size of patches on air filters and under what conditions the filter must be replaced.
  - Review smoke studies used to demonstrate air flow in the critical area.
- Review map of environmental monitoring sites if available.
  - Request information regarding sampling points chosen and action and alert level decisions. Verify justification exist for the sampling points chosen
  - Verify that the monitoring of air includes temperature, humidity, particulate count and microbial content.
    - Determine if the testing frequency has been justified and/or validated.
    - Review data to ensure that the results consistently support the required particulate and microbial standard.
    - Determine if there is continuous monitoring of air for non-viable particulates.
    - Determine if the monitoring system is validated.
    - Determine if there are an adequate number of points sampled and if there is justification for sampling the established points. This justification can be based on historical data as well as the critical operations performed in the cleanroom. Ask if the site has a formal rationale or justification statement defining the selection of testing points.
    - Ensure that the sampling time meets worldwide regulatory expectations.
    - Determine if the site performs a trend analysis on its data, and at what frequency (i.e. on a yearly basis, quarterly, monthly).
  - Ensure that there is an approved program for monitoring equipment and facility surfaces.
    - Review the data for monitoring surfaces to ensure that it is comprehensive and includes applicable equipment, walls, curtains, door plates, floors, etc.
    - Determine what method is used for monitoring surfaces (e.g. contact plate, swab) and evaluate the appropriateness.
    - Determine if there is sound justification for the number, frequency and location of surfaces that are sampled.
    - Determine when sampling takes place. Samples should be taken after a period of activity.
    - Determine if the data consistently support the required microbial limits.
    - Determine if the site performs trend analysis on its data, and at what frequency (i.e. on a yearly basis, quarterly, monthly).