Environmental Monitoring of Aseptic Processing Areas - 1

- ¨*A war against an invisible enemy*¨

Training Course Agenda

- Overview of Environmental Monitoring
- Sampling Techniques
- Action and Alert Limits
- Environmental Monitoring Laboratory Activities

Cleanrooms should be monitored for microorganisms and particles

Environmental Monitoring Program Requirements:

- Surface Monitoring
- Active Air Monitoring
- Passive Air Monitoring
- Microbiological Media and Identification
- Particle Counting

USP 1116 - MICROBIOLOGICAL CONTROL & MONITORING OF ASEPTIC PROCESSING ENVIRONMENTS

- "Recommendations for environments where the risk of microbial contamination is controlled through aseptic processing applied only to clean rooms, RABS, and isolators".

- EM Program: **"**Documented program implemented via SOPs that describes in detail methods and acceptance criteria for monitoring **particulates** and **microorganisms** in controlled environments (air, surface, personnel gear, compressed gases). Includes sampling sites, frequency of sampling, and investigative and corrective actions".

- *"ASEPTIC":* process for handling sterilized materials in a controlled environment designed to **maintain** microbial contamination at **levels** known to present minimal risk.

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- ISO 14644 series (Air grade classification with respect to the concentration of total particulates per unit volumen only. No viable particles limits).
- Consider nonviable particulate contamination in injectable products (see *Particulate Matter in Injections* 788).
- In any environment where human operators are present, microbial contamination at some level is **inevitable**.

E.M. results can neither prove nor disprove sterility.

Purpose of an Environmental Monitoring Program:

- Provides crucial information on the quality of the aseptic processing environment during manufacturing

- Prevents the release of potentially contaminated batch if appropriate standards are not fulfilled

- Prevents future contamination by detecting adverse **trends**

Why perform EM?

- Identify events that may cause a room to be dirtier than allowed:
  - Air system failure (e.g. ?.....)
  - Cleaning was not done properly (e.g. ?.....)
  - Other factors

- Processing areas are monitored to catch these problems **BEFORE** they impact the product.
- Monitoring = Detection System.
- Strong limitations: based on limited samples; Microbiological results are not immediate; Bacteria multiplies very fast.

Purpose of EM System

To demonstrate that other systems are working

- Passing EM results through time indicate that other systems are properly supporting the process and that processing is being carried out in a controlled manner:
  - HVAC
  - Facility Cleaning
  - Gowning
  - Facility
  - Other ?.....
- Failed EM results indicate that processing is nor being carried out in a controlled manner

Regulatory

FDA: *"In aseptic processing, one of the most important laboratory controls is the environmental monitoring program."*

-Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing (Sep. 2004)

EU: *"Clean rooms and clean air devices should be routinely monitored **in operation** and the monitoring locations based on a **formal risk analysis** study and the results obtained during the **classification of rooms and/or clean air devices**."*

-Eudralex, Volume 4, Annex 1: Manufacture of Sterile Medicinal Products

ISO 13408-1

ISO 13408: “Aseptic processing of health care products”

- Addresses Environmental Monitoring:

EM Program:

- Should be defined, documented, and maintained with written procedures.

- Procedures should describe:
  - Frequency of monitoring
  - Type of monitoring
  - Sites monitored
  - Alert and action levels
  - Actions taken when specifications are exceeded

Elements of EM Program

Documentation

- The EM program should be well-documented. Documents include:
  - Procedures
  - Sampling Plans
    - Risk Assessments
    - Statistical Justification
  - Testing Records
  - Investigation Records
  - Trending Reports
  - Microbiological Validation

Static or "At Rest" Monitoring

- Performed in an area when no processing is occurring
- EU regulations recommend at least a 15 minute rest period after processing to return the area to a state of rest
- Used to qualify a new / refurbished facility / maintain the area with no production / prove efficacy of sanitization agents
- Trending static monitoring results demonstrates that facility systems are in a state of control

Dynamic Monitoring

- Monitoring when the process is ongoing. Most important part of EM

- Monitoring focuses on highest-risk areas
  - Critical operations
  - High traffic areas
  - Grade A spaces

- Monitoring should not compromise the aseptic process, thus putting the patient at risk.

Quiz: Give 2 examples that show how the monitoring activity may compromise the aseptic fill:

Dynamic Monitoring

- Results are indicative of the ability of the facility to contain and support the specific process (e.g., Gowning and flows of personnel, equipment, etc.)
- If static monitoring passes and dynamic fails, the process either needs a better designed cleanroom, equipment technology, or improve cleaning and manufacturing practices
- Dynamic monitoring limits should be appropriate for the air classification and the specific process

- Should sterile powder-based processes have a different criteria than liquid processes in the aseptic fill area ?. -Address at rest and in-operation conditions

USP 1116 -ESTABLISHMENT OF SAMPLING PLAN AND MONITORING LOCATIONS

Sampling Plan:

“A documented plan that describes the procedures and methods for sampling a controlled environment; identifies the sampling sites, the sampling frequency, and number of samples; and describes the method of analysis and how to interpret the results”.

USP 1116 - -ESTABLISHMENT OF SAMPLING PLAN AND MONITORING LOCATIONS

- During initial startup or commissioning of a clean room, specific locations for air and surface sampling should be determined. (*intensive sampling*)

- Locations considered should include those in proximity of the exposed product, containers, closures, and product contact surfaces of Critical Zone (always ISO 5) WITHOUT creating contamination risk.

USP 1116 - -ESTABLISHMENT OF SAMPLING PLAN AND MONITORING LOCATIONS

- Microbiological monitoring of environments in which products (and equipment or materials) are filled or processed before terminal sterilization is generally less critical than the monitoring of aseptic processing areas.

- Classified environments in which **closed** manufacturing operations are conducted, including fermentation, sterile API processing, and chemical processes, require fewer monitoring sites and less frequent monitoring because the risk of microbial contamination from the surrounding environment is comparatively low.

(See **WHO** Environmental Monitoring of Clean Rooms in Vaccine Manufacturing Facilities: Points to consider for manufacturers of human vaccines, November 2012).

USP 1116 - -ESTABLISHMENT OF SAMPLING PLAN AND MONITORING LOCATIONS

- Mapping of the clean room during the qualification phase can provide useful information concerning the movement, positioning of personnel, and the most frequently conducted manipulations and interventions, including entry points where equipment and materials move from areas of lower classification to those of higher classification, within and around doors and airlocks, etc.

- Sampling of walls and floors based on a grid approach also provides an indication of sanitization effectiveness.

USP 1116 - -ESTABLISHMENT OF SAMPLING PLAN AND MONITORING LOCATIONS

Sampling scheme based on:

- Standard normative (eg, WHO 961) recommendations
- Prospective risk assessment and a rationale for sampling locations and frequencies (*and methods*) for each controlled environment.
- EM History / Trends
- Qualification / Requalification data
- Process (eg, duration, complexitiy, number of personnel, technology, closed/open, equipment breakdowns, handling of live organisms)

Personnel

- Personnel are monitored regularly to ensure they are not contaminating their gowns

- If an operator was clean at the end, he or she was likely clean throughout the activity

Sample Sites

FDA Guidance on Aseptically Produced Drugs:

- *"The monitoring program should cover all **production shifts** and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures".*
- *Air and surface samples should be taken at the locations where significant activity or product exposure occurs during production.*
- *It is especially important to monitor the microbiological quality of the critical area to determine whether or not aseptic conditions are maintained during filling and closing activities.*

Sample Sites

FDA Guidance on Aseptically Produced Drugs:

- *Critical surface sampling should be performed **at the conclusion** of the aseptic processing operation to avoid direct contact with sterile surfaces during processing.*

- *When identifying critical sites to be sampled, consideration should be given to the points of **contamination risk** in a process, including factors such as difficulty of setup, length of processing time, and impact of interventions.*

- Continuous total particle

Monitoring in class A

Record of Continuous total particle monitoring in class B

Total particle monitoring in UDAF

- Isocinetic sampling: Captures particles at the same speed as the velocity of the surrounding air, avoiding distorsion of the relationships between particles of different sizes. Required in laminar flow areas (90 ft/min. or 0.45 m/sec).

Isocinetic probe

Sample Frequency

- Dynamic Monitoring is required for all critical operations

Total Particles (TP)

- TP Monitoring may be a series of samples (e.g. for class C or D), or continual monitoring + series of samples (e.g. for class A and B)
  - Filling and other grade A finishing operations MUST be continually monitored for particulates.

Microbial

- Continual monitoring for microbes in class A and B should be performed; Settling plates meet this expectation.
  - Why are settling plates are recommended to monitor class A during operations rather than active air samplers ?

Sample Frequency

Eudralex Volume 4, Annex 1

- The Grade A zone should be monitored at such a frequency and with suitable sample size that all interventions, **transient events** and any system deterioration would be captured and alarms triggered if alert limits are exceeded.

Risk Assessment Analysis:

- **"**Analysis of the identification of contamination potentials in controlled environments that establish priorities in terms of severity and frequency (of occurrence) and that will develop methods and procedures that will eliminate, reduce, minimize, or mitigate their potential for microbial contamination of the product/container/closure system".

Sample Frequency

Table 3. Monitoring frequencies for *in operation* routine particulate sampling

Classification	In operation (dynamic) routine particulate sampling
Grade A (filling operation)	For the full duration of operation
Grade B	Daily[1]
Grade C	Weekly
Grade D	Not required
UDAF work stations in B	Daily [(1)]
UDAF work stations in C	Weekly
UDAF work stations in D	Monthly
UDAF in UNC areas	Routine re-qualification of UDAF is sufficient

[(1)] Working days. Monitoring can be omitted on e.g., weekends if no production activities are taking place.

TIPS for Sampling Decisions

- **Know** your facility and process
- **Assess** your facility and process for risks and function
- Develop a plan that is **appropriate** for your facility and process
- **Document** your decisions so you can defend them to regulators

Air Particulate Monitoring

- Provides immediate results
  - Serves as a go / no-go decision point
- Does not differentiate between viable and non-viable particles
- The scattering of laser light by each particle shows the size and number of particles

Annex 1 UE:

- “Airborne particle monitoring systems …Where remote sampling systems are used, the length of tubing and the radio of any bends in the tubing must be considered in the context of particle losses in the tubing”.

Air Particulate Monitoring

3.2.3 Particulate sampling methods[3]

14. Sampling procedures may be conducted by quality control, quality assurance, production personnel, or other designated personnel or contractors with specialized training and skills to conduct the activity.

15. Particles should be measured by a light-scattering instrument designed to detect airborne particles of defined sizes in a clean room environment. The instrument should have a valid calibration certificate, with the frequency of calibration dependent on the type of instrument and its use; the manufacturer's instructions for calibration and set-up provide valuable information in this regard. Particles of the two size ranges stated in the WHO requirements must be analysed. Isokinetic sample heads should be used in unidirectional airflow systems.

3.2.5. Routine monitoring for particulates

For each clean room, companies should conduct an analysis of the layout of the room, the materials, equipment, and personnel present, the types of activities conducted, and the potential risk to the product. From this analysis, a risk-based routine sampling plan detailing sampling sites, volumes, and frequencies can be devised; this plan, a schematic drawing of the room showing sampling locations, and a justification of the choice of sampling locations should be clearly documented. Risk assessments should be kept up to date. Modifications to the area risk assessment and sampling plan should reflect EM results that indicate unsuspected areas of contamination or dispersion. Additionally, in new, renovated facilities or after plant shutdowns, additional sampling is recommended to find possible locations where contamination is recurrent.