ENVIRONMENTAL MONITORING FUNDAMENTALS

OCTOBER 19, 2023
AMANDA CURTIS
MICROBIOLOGY CONSULTANT, VALSOURCE

RestoreSight.org

1

INTRODUCTION

- BS in Microbiology from Purdue University
- 15 years experience between clinical microbiology and aseptic processing
- Focus on ATMPs, HCT/Ps, and aseptic processing of sterile drugs
- Current contributor to multiple ASTM and PDA guidance documents

Amanda Curtis
Microbiology Consultant
414-460-3471
acurtis@valsource.com
VALSOURCE
Innovative Solutions. Sustainable Results.

RestoreSight.org

2

AGENDA

- Regulatory expectations for an EM program
- Environmental Monitoring basics – the "How"
- Risk-based approach to designing and maintaining an EM program, including the "When" and "Where"
- How and when to re-qualify the EM program and personnel gowning

To be covered in Webinar 2: Setting Alert levels and Action limits, how and when to trend EM data, how to recognize and investigate adverse trends and EM excursions.

RestoreSight.org

3

REGULATORY EXPECTATIONS

4

REGULATORY REQUIREMENTS

Code of Federal Regulations (CFR)

- Title 21 – Food and Drugs
  - Chapter I: Food and Drug Administration, Department of Health and Human Services
    - Subchapter L: Regulations Under Certain Other Acts Administered by the Food and Drug Administration
      - Part 1271: Human Cells, Tissues, and Cellular and Tissue-Based Products
        - **Subpart D: Current Good Tissue Practice**

§1271.195 Environmental Control and Monitoring

(c) ***Environmental monitoring.*** You must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms.

RestoreSight.org

5

REGULATORY GUIDANCE

- FDA Guidance for Industry: Validation of Procedures for Processing of Human Tissues Intended for Transplantation (2002)
- **FDA Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (2011)**
  - Refers the reader to FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (2004)
- European Commission "Annex 1: Manufacture of Sterile Medicinal Products, EudraLex – Volume 4 – EU Guidelines to Good Manufacturing Practice, Medicinal Products for Human and Veterinary Use" (2022)

FDA HCT/P Guidance

FDA Aseptic Guidance

Annex 1

RestoreSight.org

6

INDUSTRY GUIDANCE

The "c" in cGMP

- **United States Pharmacopeia 42 - <1116>:** Microbiological Control and Monitoring of Aseptic Processing Environments. (2013)
- **PDA Technical Report #13:** Fundamentals of an Environmental Monitoring Program (2022)
- **PDA Technical Report #88:** Microbial Data Deviation Investigations (2022)
- **ISO 14644-1:** Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness by particle concentration (2015)
- **ISO 14644-2:** Cleanrooms and associated controlled environments – Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration (2015)
- **ICH Q9**: Quality Risk Management (2022)
- **ICH Q10**: Pharmaceutical Quality System (2008)

Note: ISO 14644 only provides guidance for cleanroom classification. Not routine EM!

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

7

ENVIRONMENTAL MONITORING BASICS

8

WHAT IS EM?

Environmental Monitoring: The monitoring of a controlled environment to demonstrate that the area is in a state of control, to detect excursions and trends, to assess effectiveness of cleaning, and to monitor personnel.

Monitoring also covers water systems, temperature, relative humidity, and differential pressure.

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

9

WHAT IS EM AND WHAT DOES IT DO?

Environmental monitoring (EM): The monitoring of a controlled environment.

EM Does:

- Identify problems in a facility or process
- Identifies trends and individual events
- Gathers data to support root cause analysis
- Assesses effectiveness of cleaning and disinfection
- Evaluates the aseptic processing environment

EM Does Not:

- Control or prevent contamination
- Recover or detect **all** contamination that is present
- Prove product sterility or non-sterility

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

10

EM SAMPLING: REGULATORY GUIDANCE

All the relevant regulatory and industry guidances recommend use of all the below methods in classified spaces:

- Total particulate air monitoring (aka non-viable particulate)
- Viable particulate air monitoring (active and/or passive methods)
- Surface monitoring (contact plates and/or swabs)
- Personnel monitoring

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

11

EM SAMPLING: TOTAL PARTICULATES

- Discrete laser particle counting technology
- Fixed or portable equipment
- Continuous or intermittent monitoring
- Fixed sampling rates (LPM, CFM, or m^3)
- Varying sampling volumes (0.2-1m^3)
- Isokinetic probes/funnels sized according to flow rate
- Monitors ≥0.5µm and ≥5.0µm particles

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

12

EM SAMPLING: TOTAL PARTICULATES

Guidance Document*	Recommended Particle Sizes	
	≥0.5µm	≥5.0µm
FDA Aseptic Processing Guidance	X	
USP <1116>	X	
ISO 14644 (Room classification only)	X	
PDA TR 13	N/A – Comparison only	
EMA Annex 1	X	X

EM programs commonly measure both ≥0.5µm particles and ≥5.0µm particles, as these are the most common particle sizes microorganisms will attach to.

- ≥0.5µm particles: Behave like air molecules and can remain suspended indefinitely. Tests cleanroom and HEPA control.
- ≥5.0µm particles: Settle out of air quickly and stay close to where they were generated. Associated with humans, equipment malfunction, residues, fungi.

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

13

EM SAMPLING: ACTIVE VIABLE AIR

- Actively pull air onto solid medium, which is then incubated and inspected for growth
- Fixed or portable equipment
- Fixed flow rates (CFM or LPM)
- Total volume of air/sampling time set by user
- Note need to disinfect unit and sampling head between sampling locations

Recovery rate varies with device used up to •3-fold.

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

14

EM SAMPLING: PASSIVE VIABLE AIR

Recovery rate ~1/4 that of active methods

- AKA "Settle plates." Recover viable contamination that "settles" on to the agar surface
- Results are qualitative or semi-quantitative
- Can be positioned close to the areas that pose the greatest risk of product contamination
- Can be useful when considered in conjunction with active air and surface monitoring

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

15

EM SAMPLING: SURFACE (CONTACT PLATES)

- 25cm^2 petri dishes filled with disinfectant-neutralizing media. Commonly called "RODAC" plates
- Convex surface that must be "rolled" on the surface to fully contact
- Quantitative
- Leave a residue that must be removed
  - Not suitable for irregular surfaces, but also used for personnel monitoring

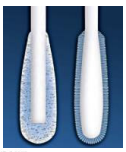
Recovery rate: 0-80%

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

16

EM SAMPLING: SURFACE (SWABS)



Recovery rate: 13-56%

- Swabbing technique requires detailed training
- Used for irregular or small surfaces
- Material can be spun, flocked, or sponge
- Processing can be direct to agar/broth, pour plate, or filter
- Swabs must be wet

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

17

RISK-BASED APPROACH TO AN EM PROGRAM

18

WHAT IS AN EMPQ?

An **EM Performance Qualification (EMPQ)** is based on Quality Risk Management principles and is used to qualify the cleanroom. It provides the risk-based justifications for the decisions made when designing your EM program.

Scientific justification for the position of the permanent non-viable monitors in the critical adjacent grade A areas was not provided.

Your airborne particulate monitoring program for aseptic filling operations is not designed and conducted to provide meaningful data to support the quality of your drug products intended to be sterile. You do not monitor airborne particulates to ISO 5 air classifications in all critical locations; the frequency of airborne particulate monitoring is not adequately supported; and the orientation of particle counter probes is not directed into the flow of air in monitored locations.

(A) The firm does not routinely perform viable and nonviable environmental sampling in classified rooms or hoods during the production of drug products prepared pursuant to patient-specific prescriptions.

Additionally, the door handles of the cleanroom, the handles of the (b) (4) door, and the computer keyboards in the anteroom and (b) (4) room, which are frequently touched with gloved and ungloved hands during operations, are not included in the firm's environmental monitoring program without justification.

EYE BANK ASSOCIATION OF AMERICA

19

WHEN ARE EMPQS REQUIRED?

EMPQs are required:

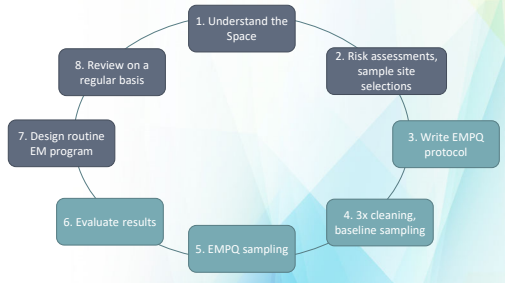
- Startup of a new facility/cleanroom
- After planned/unplanned room shutdowns
- Requalification after modification of controlled classified areas
  - Changes to room layout
  - Process flow changes
  - Change to room use
  - Changes in EM data trending

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

20

GENERAL OVERVIEW



EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

21

7. DESIGN ROUTINE EM PROGRAM

Does not describe an EM program; not in alignment with other guidances

What about total particulates?

Grade	EBAA Medical Standards (2023)	FDA Aseptic Guidance	USP <1116>	Annex 1
A	Either: a) Meets ISO 5 standards b) Accredited operating room OR c) Documented annually to have <25 CFU/90mm settle plate over 1 hour.	• Total particulate during production • Viable air during production • Surfaces at end of process • Personnel daily/with each lot	• Active air each shift • Surfaces at end of process • Personnel at completion of work	• Continuous total particulate • Continuous viable air (combination active and passive) • Surfaces at end of process • Personnel periodically and at end
B	Not specified	Not specified	All sampling each shift	• Frequent or continuous total particulate and viable air • Surfaces at end of process • Personnel at end
C	Not specified	Not specified	All sampling once/day	Based on risk assessment
D	Not specified	Not specified	All sampling once/day	Based on risk assessment

What about B/C/D?

This seems like a lot for C/D

What does "all sampling" mean? Personnel?

EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

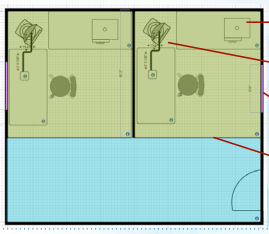
22

1. GAIN AN UNDERSTANDING OF THE SPACE

Create your risk assessment team consisting of folks familiar with microbiology, tissue processing, facilities, quality risk management, and quality assurance. You will also need a detailed map of the space.

Grade A/ISO 5

Grade B/ISO 7



EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

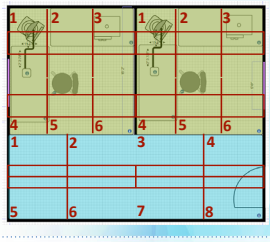
23

1. GAIN AN UNDERSTANDING OF THE SPACE

Divide the room(s) into grids per ISO 14644-1.

Grade A/ISO 5

Grade B/ISO 7



EYE BANK ASSOCIATION OF AMERICA

RestoreSight.org

24

1. GAIN AN UNDERSTANDING OF THE SPACE

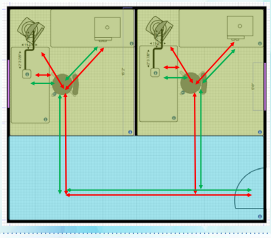
Walk the process with the team to understand personnel and material flow, what activities occur in each grid space, and what risks are in each grid space.

Grade A/ISO 5

Grade B/ISO 7

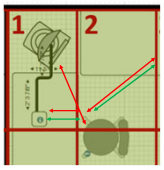
Personnel

Material



25

1. GAIN AN UNDERSTANDING OF THE SPACE



Grid	Activities in This Grid	Potential Source of Contamination	Notes
1	Corneal processing, equipment and microscope use, heavy personnel and material presence	Equipment difficult to clean, tissue, heavy personnel and material presence	Solid HEPA coverage in ceiling
2	Chair for processing, transport of materials and tissue, heavy personnel and material flow	Heavy personnel and material presence, chair wheels difficult to clean	Solid HEPA coverage in ceiling

26

2A. PERFORM YOUR RISK ASSESSMENT(S)

Choose your risk assessment tool. The most commonly used tools are the Failure Mode and Effects Analysis (FMEA) and the Hazard Analysis and Critical Control Points (HACCP).

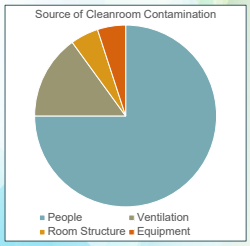
FMEA	HACCP
Process-based: What within the process is vulnerable?	Hazard-based: What could impact the process from outside?
Semi-quantitative, assigning numbers for Low/Medium/High risk and ranking the risks.	Qualitative, evaluates each risk individually.
Tool produces a list of risky grids with potentially artificial risk ratings.	Tool produces a list of risks and provides the prompt to control/mitigate the risks before monitoring each site.

27

2A. PERFORM YOUR RISK ASSESSMENT(S)

No matter which tool you use, you need to assess each grid sector based on these factors:

- Cleanability
- Personnel presence and flow
  - Look at need for and frequency of operations
- Material presence and flow
- Proximity to exposed tissue or tissue-contact materials

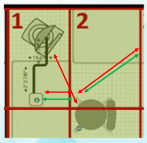


28

2B. SAMPLING SITE SELECTIONS

General Considerations

- Focus on higher-risk areas and areas that are critical to ensuring quality and patient safety.
- There are required sampling types and locations (ex. within Grade A) in the regulations to consider



Sierra Donor Services Eye Bank

29

7. DESIGN ROUTINE EM PROGRAM

Recommended: Base your routine EM program on the risk assessment and EMPQ and add/remove samples based on the results.

Not recommended: Copying and pasting your EMPQ sampling plan right into your EM procedure without evaluation.

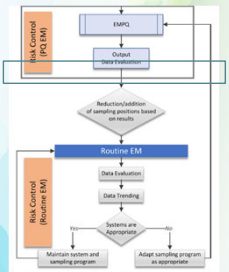


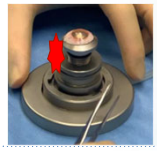
Fig. 5.2.1-1, PDA TR 13

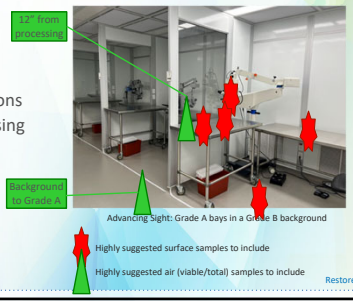
30

7. DESIGN ROUTINE EM PROGRAM: SAMPLE SITES

Sample Sites:

- High risk areas
- EMPQ samples with excursions
- Historical samples with excursions
- Close to exposed tissue processing





RestoreSight.org

31

7. DESIGN ROUTINE EM PROGRAM: FREQUENCY

Base frequency of sampling on risk!

EM data during tissue processing is **required**.

Example sampling plan:

	Grade A	Grade B	Grade C (Support only)	Grade D (Support only)
In Operation	• Continuous total particulate • Continuous passive air • Active air at critical steps • Surfaces at end of process • Personnel periodically and at end of process	• Total particulate and active air at beginning and end of aseptic process • Surfaces at end of aseptic process • Personnel at exit of room	N/A	N/A
Static	Once per week: • Intermittent total particulate • Active air • Surfaces	Once per week: • Intermittent total particulate • Active air • Surfaces	Every other week: • Intermittent total particulate • Active air • Surfaces	Every other week: • Intermittent total particulate • Active air • Surfaces

RestoreSight.org

32

8. REVIEW ON A REGULAR BASIS

Update risk assessment, perform EMPQ, and evaluate routine EM program:

- Predefined routine basis
- In response to shifts detected in routine EM data trending
- Adverse trends or events
- Major changes to process or area

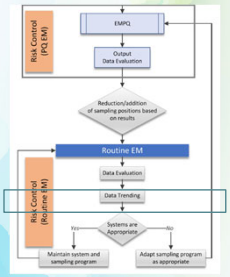


Fig. 5.2.1-1, PDA TR 13

RestoreSight.org

33

PERSONNEL QUALIFICATION AND MONITORING

34

INITIAL GOWNING QUALIFICATION

See Annex 1 Section 7

Initial Training

- Personal hygiene
- Microbiology, sterility assurance
- Patient safety hazards posed by contaminated product
- Aseptic techniques
- Appropriate cleanroom behavior
- Gowning certification

Gowning Certification

- Hands-on supervised gowning practice
- 3x passing gowning qualification in the cleanroom environment
- Set strict limits (ex. <1 CFU)
- Monitor gown locations closest to processing, difficult to handle during gowning
  - Gloves
  - Forearms
  - Chest

Consider other locations:

- Hood/forehead
- Goggles

RestoreSight.org

35

PERIODIC RE-QUALIFICATION

When?

- On a routine basis, at least annually
- After extended absences
- Corrective action for adverse trends in personnel monitoring

What?

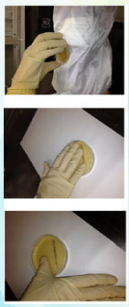
- Same sample sites as for initial qualification
- 1x sampling for routine re-qual acceptable
- 3x sampling recommended for return from extended absences or adverse trends

RestoreSight.org

36

ROUTINE MONITORING

- Define sampling locations by risk assessment. Most common for Grade A LFHs/BSCs is gloves and forearms.
  - **Grade A bays or rooms may require additional personnel samples.**
- Use contact plates for sampling, not swabs.



37

IN CONCLUSION…

- The entire EM program must be risk-based, scientifically justified, and documented.
- Design and ownership of the EM program must be done by a project team.
- **Don't be scared.** You are the experts in your process, and this activity provides a structured way to document what you already know.

38

QUESTIONS?

39

THANK YOU FOR ATTENDING!

40