U.S. FOOD & DRUG ADMINISTRATION

Environmental Monitoring for Compounding Facilities

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Learning Objectives:

- Define environmental monitoring and its significance in ensuring product quality and patient safety
- Describe statutory requirements for compounding pharmacies (503A) and outsourcing facilities (503B)
- Explain regulatory requirements and the agency's expectations
- Identify types of monitoring specific to environmental monitoring
- Recognize concepts related to design and implementation of environmental and personnel monitoring programs

Topics of Discussion

- What is Environmental Monitoring?
- Statutory requirements
- Regulatory requirements and expectations
- Types of monitoring

FDA Guidance:

- FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)
- FDA Guidance for Industry: Insanitary Conditions at Compounding Facilities. (2020)
- FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act which, when finalized, will reflect FDA's current thinking on compliance with CGMP requirements for 503B facilities. (2020)

What is Environmental Monitoring (EM)?

EM includes tests, assays, and measurements used in controlled environments to detect **events**, **trends**, or **changes** in viable microbial flora (i.e., counts, types), total particle counts, temperature, differential pressure, or humidity.

Aseptically Processed

Terminally Sterilized

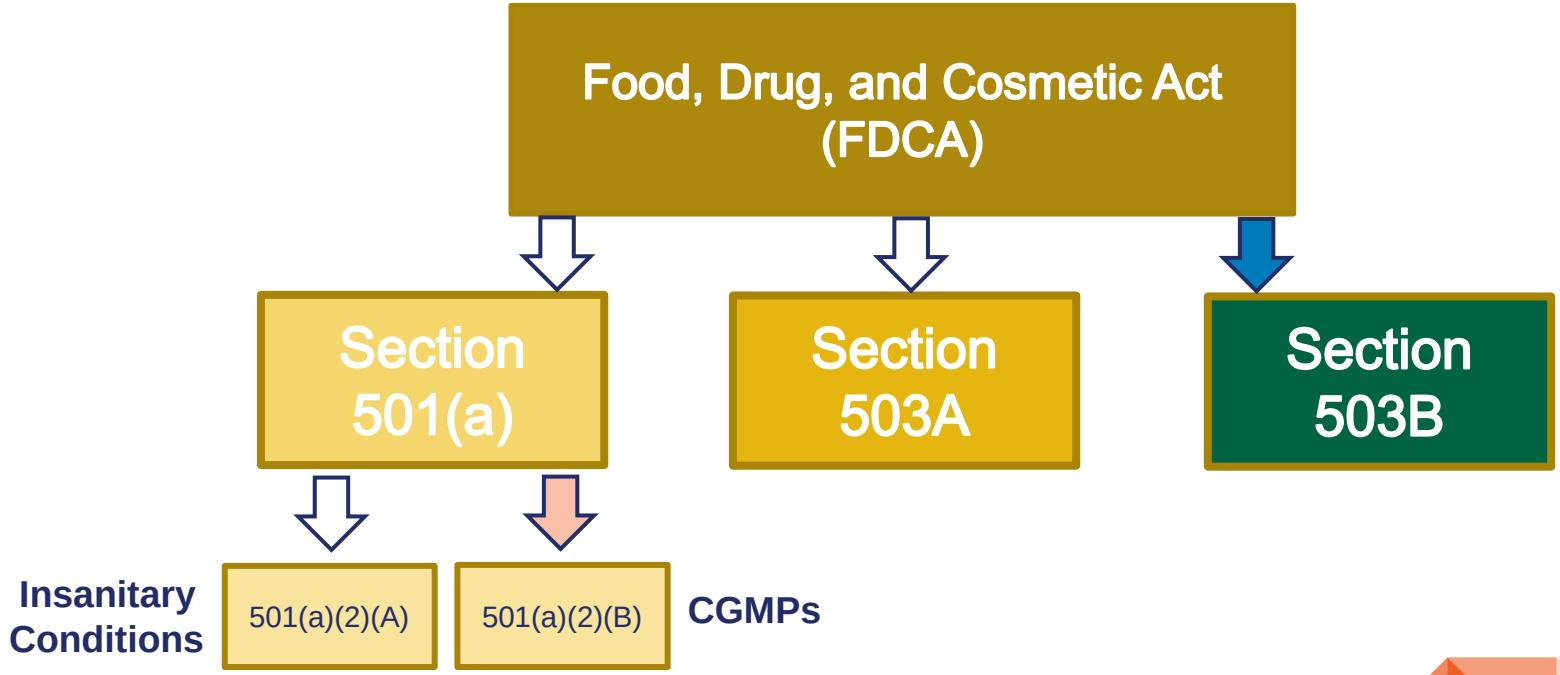
What is Environmental Monitoring used for?

- Provides information about the quality of the production environment
- Provides information on effectiveness of facility controls (e.g., HVAC system)
- Provides information on personnel engaged in aseptic processing (e.g., fingertip testing, gowns)
- Provides information on effectiveness of the cleaning and disinfection program
- Identifies potential routes of contamination allowing corrective actions to be implemented before product/patients are adversely impacted

Environmental Monitoring (EM) is **NOT**:

- A release test
- Precise or reproducible
- Representative (e.g., surface, cleanroom, controlled area)
- Definitive proof of cause/effect
  - 2004 FDA GFI Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice states “Detection of microbial contamination on a critical site would not necessarily result in batch rejection. The contaminated critical site sample should prompt an investigation of operational information and data that includes an awareness of the potential for a low incidence of false positives.”

Statutory Requirements for 503A Facilities and Outsourcing Facilities (503B)



Section 501(a) of the FDCA

Section **501(a)(2)(A)** of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a drug is deemed to be **adulterated** "if it has been prepared, packed, or held under **insanitary conditions**

(1) whereby it may have been **contaminated with filth**, or
(2) whereby it may have been rendered **injurious to health**."

Example of **contaminated with filth** includes non-microbial contamination, microbial contamination, chemical contamination, or contamination other than microbial introduced by vermin (e.g., hair, insect body parts).

Section 501(a) of the FDCA

Section **501(a)(2)(B)** of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a drug is deemed to be **adulterated** "if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with **current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess."

Example of CGMPs - 21 CFR 210 and 211 requirements:

- Procedures
- Documentation
- Qualification/Validation
- Controls: materials/facility/process/personnel

Section 503A of the FDCA

Drug products that meet the requirements of section 503A are exempt from sections **501(a)(2)(B)**, 502(f)(1), and 505 of the FDCA. Certain provisions in 503A address:

- Preparation by licensed pharmacist or physician
- Preparation for individual patient based on receipt of valid prescription
- Anticipatory compounding
- Use or bulk drug substances
- Copies

Drugs prepared in accordance with section 503A of the FDCA are **exempt** from CGMP requirements.

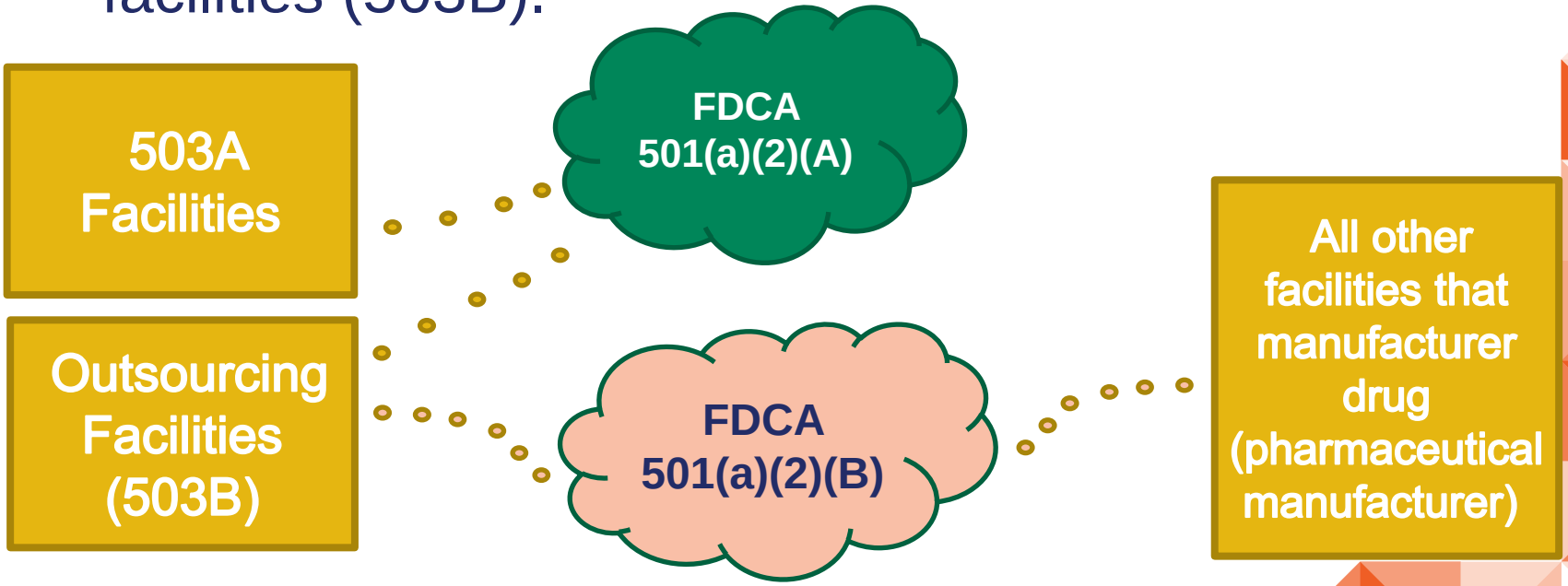
Section 503B of the FDCA

Provides exemptions from sections 502(f)(1), 505, and 582 of the FDCA for drugs that are compounded by or under direct supervision of a licensed pharmacist in a facility that has registered as an outsourcing facility. Certain provisions in 503B address:

- Labeling (not including directions for use)
- Adverse event reporting
- Bulk drug substances
- Copies
- Drug reporting
- Prohibition on Wholesaling

Drugs prepared in accordance with section 503B of the FDCA must **meet** CGMP requirements.

The exemptions in sections 503A and 503B are the basis for the **differences** in the regulatory expectations for 503A facilities and outsourcing facilities (503B).



Regulatory Expectations for Environmental Monitoring – 503A Facilities and Outsourcing Facilities (503B)

- FDA GFI titled Insanitary Conditions at Compounding Facilities states, FDA has observed the *lack of adequate environmental monitoring* as an insanitary condition.
  - *Footnote 15 of this guidance, explains that EM provides information about the quality of the aseptic processing environment, and corrective actions should be taken when potential routes of contamination are identified.*

Regulatory Expectations for Environmental Monitoring – 503A Facilities and Outsourcing Facilities (503B)

503A & 503B	503B Only
Compounded drugs are not exempt from section 501(a)(2)(A) of the FDCA. - Insanitary Conditions	**Compounded drugs prepared at outsourcing facilities are not exempt from section 501(a)(2)(B) of the FDCA. - CGMP**
*All compounders including both compounding facilities and outsourcing facilities **should** perform environmental monitoring AND implement corrective actions when monitoring data indicates the drug production environment has been compromised.*	*Outsourcing facilities **must** perform environmental monitoring and **investigate any failures** AND implement corrective actions when monitoring data indicates the drug production environment has been compromised.*

Regulatory Expectations for EM – Outsourcing Facilities (503B)

21 CFR 211.42(b) addresses the design and construction of facilities used to manufacture, process, pack, or hold drug products. Buildings should be of adequate size and designed to prevent mix-ups or contamination.

Regulatory Expectations for EM – Outsourcing Facilities (503B)

21 CFR 211.42(c) states in part: “Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm’s operations as are necessary to prevent contamination or mix-ups during the course of the following procedures:

(10) Aseptic processing, which includes, as appropriate:
(iv) A system for monitoring environmental conditions”

Types of Tests, Assays, Measurements

- Non-viable particle counting (air)
- Viable particle counting (air, surfaces)
- Personnel Monitoring (glove, gown)
- Differential Pressure
- Temperature
- Humidity

Environmental Monitoring Program

- Sampling methods may be based on risk and peer-reviewed literature.
- Sampling locations should be supported by a scientific justification based on risk.
- EM should be performed for sterile and non-sterile production operations.
- Frequency of monitoring should be commensurate with risk.

Recommendation for how **frequently** environmental monitoring should be performed differs for 503A and 503B facilities and **should be commensurate with risk.**

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Environmental Monitoring Program: Monitoring Frequencies

Sterile Drug Production (CGMP)	Non-Sterile Drug Production (CGMP Only)
• During production, at least once per shift, monitor the ISO 5 area at least daily • Monitor ISO 5, ISO7, ISO 8, CNC areas • Typically performed by OF staff • Gloves testing with each batch; test strategic locations on gowns • Frequent monitoring, alarm systems to notify staff when parameters are out of specification	• Commensurate with risk; monitor temperature and humidity daily, viable particle counts quarterly. **Note**: These recommendations are suggested monitoring frequencies for outsourcing facilities 503B facilities that follow CGMP requirements. How **frequently** environmental monitoring should be performed differs for 503A and 503B facilities.

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Environmental Monitoring: Non-viable Particles

- Non-viable particles such as dust, paint chips, hairs, fibers, glass, etc., may be found in the air or on surfaces.
- Why do we care about non-viable particles?
  - Represent a type of filth
  - Vehicles for microbial particles

Environmental Monitoring: Non-viable Particles

- Particularly, the air particles are assessed using technology that cannot determine whether said particles have microbes adhering to the its surface.
- ISO 14644-1:2015 defines limits for 0.5µm (or larger) particles in air.

Table 1. ISO Classification of Particulate Matter in Room Air*

ISO Class Name	Particles/m^3
3	35.2
4	352
5	3,520
6	35,200
7	352,000
8	3,520,000

*Limits are in particles of 0.5 µm and larger per cubic meter (current ISO) measured under dynamic conditions. Adapted from ISO 14644-1:2015, Cleanrooms and associated controlled environments—Part 1: Classification of air cleanliness by particle concentration.

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

How are non-viable particles counted?

Fixed/remote counters

Portable counters

Where should non-viable particles be counted?

2004 FDA GFI titled Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice recommends:

- Measurements to confirm air cleanliness in **critical areas** be taken at sites where there is the **most potential** **risk** to the exposed sterilized product, containers and closures.

- Counts should be taken at **representative locations** normally not more than 1 foot away from the work site, within the air flow.

- Particle counting probe should be placed in an orientation demonstrated to obtain a meaningful sample (i.e., in the direction of airflow).

Points to Consider: NVP Sampling Site Selection

- Proximity to filling & closing activities
- Direction of airflow
- Orientation of the probe

Do you see anything wrong in this photograph?

483 Observation

OBSERVATION 4

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

The monitoring for non-viable particulates is not located in close proximity to the aseptic operator located on the (b) (4) side of the laminar flow hood performing aseptic manipulations. The particle counter is located on the (b) (4) of the (b) (4) laminar flow hood. Two operators work simultaneously on the right and left side of the bench. The non-viable particle counter position is not in close proximity of the aseptic manipulations for the aseptic technician on the (b) (4) side of the laminar flow hood.

483 Observations

B) Environmental monitoring in the aseptic processing area has not been performed since October 2018. The last time your vendor performed active air sampling in the ISO 5 Cleanroom hood and ISO 5 IV hood was on 10/26/2018. Fungal contamination (1 CFU) was detected in the ISO 5 Cleanroom hood during this sampling. Since then, you have not implemented a program to routinely monitor environmental conditions in the aseptic processing area.

OBSERVATION 1

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically, your firm has not monitored total particle counts (b) (4) during production in the ISO 5 area between 03/02/2020 to 10/02/2020. In that time, you produced (b) (4) batches and distributed (b) (4) batches for patient use.

When should non-viable particles be counted?

- Aseptic sterile drug production environments should be monitored at least daily during production.
- Monitoring should cover all production shifts and include monitoring **during normal production conditions**.
- Include at least daily monitoring of the ISO 5 zone during operations.

Note: These recommendations are suggested monitoring frequencies for outsourcing facilities that follow CGMP requirement. How **frequently** non-viable particles should be performed differs for 503A and 503B facilities and should be commensurate with risk.

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Challenge Question

True or False?

Insanitary Conditions, (501(a)(2)(A)), are not applicable to outsourcing facilities (503B), only CGMPs, (501(a)(2)(B)), are applicable.

Challenge Question

True or False?

The viable particle limit for an ISO 5 classified area is 1 colony forming unit (CFU).

Thank you!

Doan-Trang Vuong

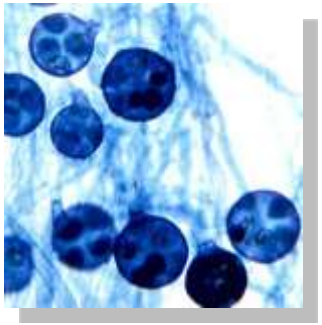
Consumer Safety Officer

Will guide you through the rest of the presentation.

Environmental Monitoring: Viable Particles

Bacteria (***Escherichia coli***)

Yeast (***Tinea pedis***)



Mold (***Saprolegnia***)

- Ubiquitous; found in the air, on surfaces, on/in people
- Microbial contamination may be visible or non-visible
- Drains, sinks, and water can be sources of microbial contamination
- Concern for drugs that are intended to be sterile
- Concern for non-sterile drugs

Why Do We Care About Viable Particles?

Microbial contamination of non-sterile drugs

- Pathogenic organisms (e.g., Salmonella typhimurium)
- Opportunistic organisms (e.g., Burkholderia cepacia)

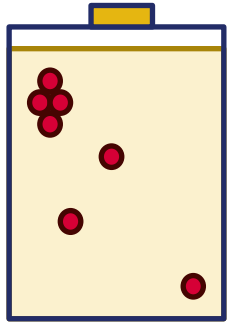
Microbial contamination of sterile drugs

- Visible microbial contamination in or adjacent to the production areas is an insanitary condition

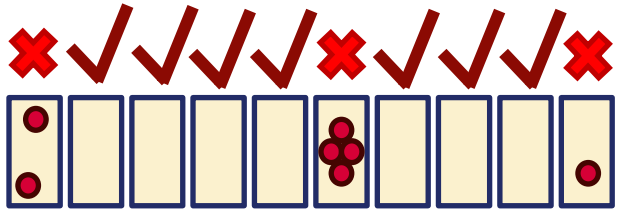
FDA GFI titled Insanitary Conditions at Compounding Facilities states that “Compounding facilities producing purportedly sterile drug products under insanitary conditions should not rely upon or cite a passing sterility test result as an indication of product sterility. Microbial contamination, when present, is not uniformly distributed within a batch; therefore, it may not be identified in a sterility test. Compounding facilities must correct all insanitary conditions at their facility regardless of whether the drugs pass a sterility test.”

Limitations of Sterility Testing

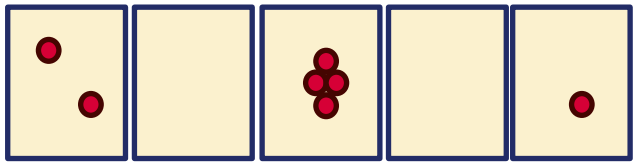
Microbial contamination is not uniformly distributed…
in a product…
…or in a sample



100 ml



10 x 10 ml samples

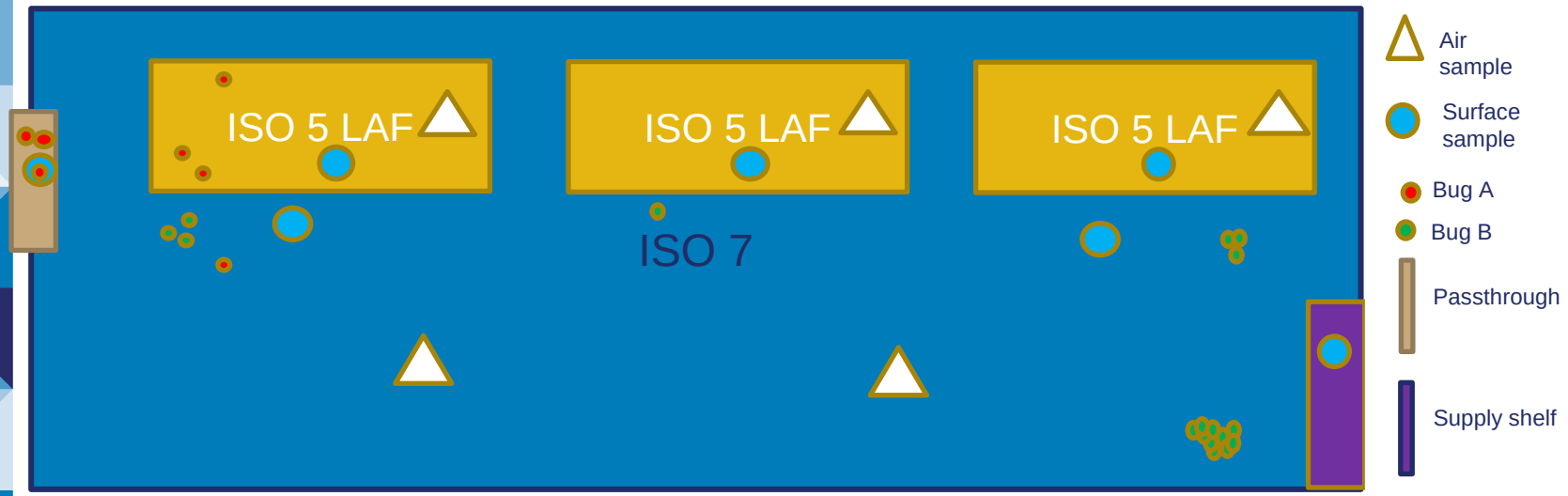


5 x 20 ml samples

Sample size matters

Limitations of Environmental Sampling

Microbial contamination is not uniformly distributed on surfaces
… or in the air



Sample location, type, and number matters

Microbial Testing is Complicated

Growth-based assays require the microbes to grow…

TSA?

30-35°C then 20-25°C?

3 days?

SDA?

30°C?

20°C?

MacConkey?

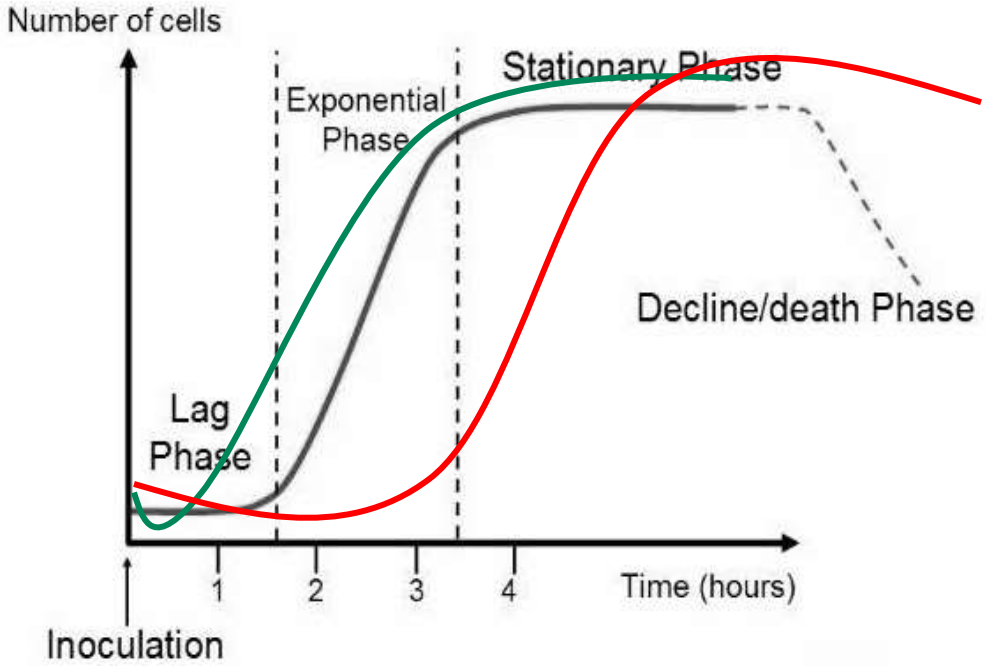
R2A?

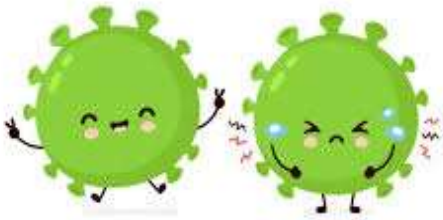
20-25°C then 30-35°C?

7 days?

Many different types of bugs, growth requirements may differ (e.g., media/nutrient requirements, optimal temperature, optimal time)

Additional Complications with Microbial Testing

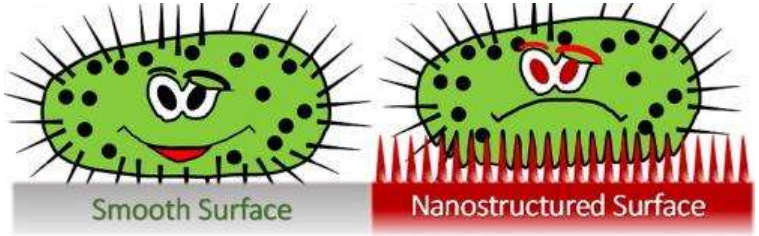


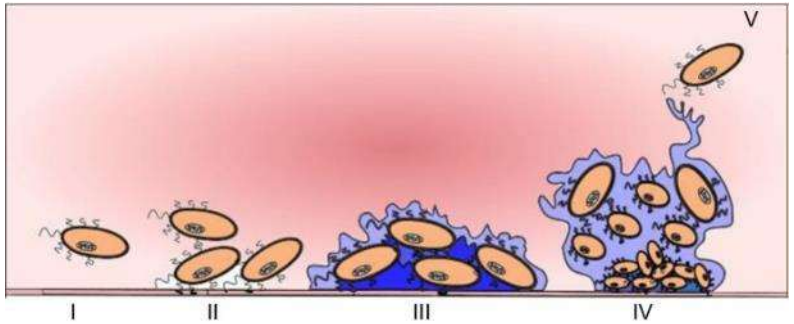


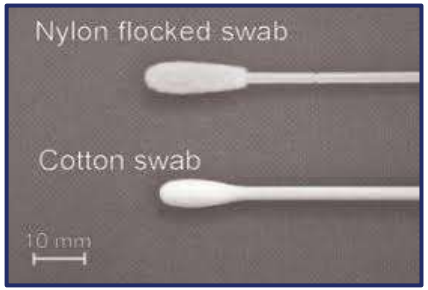
Some bacteria are healthy and can readily grow and divide. Others may be starved, dehydrated, or otherwise damaged and require some time to recover before entering the exponential growth phase.

Even More Complications with Microbes

Recovery of microbes from the environment is not reproducible







Interpreting Results of Microbial Testing

- Because there are MANY variables to consider, the results are not as precise as for analytical testing (e.g., HPLC testing, identity testing)
- Alert and Action levels should be established based on data collected in your facility.
- 2004 FDA GFI titled Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice defined Alert and Action levels as:
  - **Alert Level -** An established microbial or airborne particle level giving early warning of potential drift from normal operating conditions and triggers appropriate scrutiny and follow-up to address the potential problem. Alert levels are always lower than action levels.
  - **Action Level** - An established microbial or airborne particle level that, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

What Does Microbial Testing Data Tell Us?

- Qualitative result indicating presence of contamination
  - Does not tell you contamination is absent – even if no contamination is detected!
- Single recovery events may be significant
- Adverse trends are significant
- 503A – take corrective action to remediate microbial contamination
- 503B – OFs should investigate root cause and implement CAPA as needed

Methods Used To Monitor Viable Particles in Air

Active air sampling – compounding facilities and outsourcing facilities should perform active air sampling using devices that can quantify the number of viable microbes per volume of air sampled.

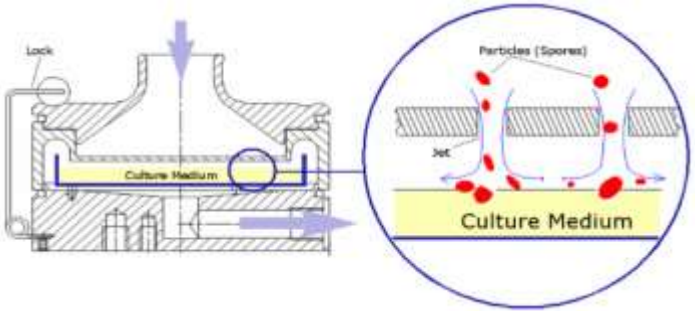
- These devices may be portable or fixed (remote).

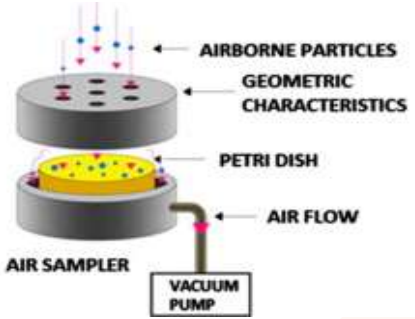
Passive air sampling – samples viable microbes in the air over a defined time period (NMT 4 hours). This is a semi-quantitative test method.

- The use of settle plates is optional.

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

Devices Used to Actively Monitor Viable Particles in Air





Tools Used To Detect Microbial Contamination on Surfaces

- Contact plates
- Sponges
- Swabs

2004 FDA GFI titled Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice states “Media used for environmental monitoring should not be exposed to decontamination cycle residues, as recovery of microorganisms would be inhibited.”

Use of Neutralizing Agents or Methods

Interfering Substance	Potential Neutralizing Agents/Method
Glutaraldehyde, mercurials	Sodium hydrogen sulfite (Sodium bisulfite), Tween
Phenolics, alcohol, aldehydes, sorbate	Dilution, Tween, Polysorbate 80, Lecithin
Aldehydes	Glycine, Tween
Quaternary ammonium compounds (QACs), parahydroxybenzoates (parabens), bis-biguanides	Lecithin
QACs, iodine, parabens	Polysorbate, Tween
Mercurials	Thioglycollate, Tween
Mercurials, halogens, aldehydes	Thiosulfate, Tween
EDTA	Mg or Ca ions

Reference USP <61> Table 2

Note: Beta-lactamases may be used when this class of antibiotics are produced. Hydrogen peroxide can be neutralized with pyruvate or catalase; peracetic acid can be neutralized with phosphate buffer. Bleach (sodium hypochlorite) can be neutralized with sodium thiosulfate ($Na_2S_2O_3$).

Rapid Microbiological Test Methods

- Some methods are growth independent: For example, Scan RDI relies on detection of fluorescent dye taken up by viable cells. Non-viable particles may also fluoresce, so presence of microbial contamination must be verified through microscopic observation.

- Other methods are dependent on growth: For example, the BacT method uses media to culture any microbes that may be present. Carbon dioxide generated by dividing bacteria causes a color change in the media that is detected by a sensor (long before turbidity can be visually detected).

Personnel Monitoring – Why is this Performed?

- Personnel can significantly affect the quality of the environment in which sterile products are processed.
- A vigilant and responsive program should be established. Monitoring should include sampling the gloves (i.e., fingertips) and other strategically selected locations of the gown of operators at an appropriate frequency, commensurate with risk.
- A more comprehensive monitoring program should be established for operators involved in operations which are more labor intensive (e.g., require repeated or complex aseptic manipulations).

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

Personnel Monitoring Program: Glove Testing & Gowning for Outsourcing Facilities (503B)

Glove Testing During Routine Operation
Glove testing with each batch (monitored daily, for each shift)
Gowning Competency including Glove Testing
Glove testing and strategic locations on sterile gowns during initial gowning qualification and at least annually.
Establish appropriate frequency for monitoring other critical sites of the gown (e.g., sleeves/forearms)

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Personnel Monitoring Program: Outsourcing Facilities (503B)

Outsourcing Facilities (503B) should also:

- Establish limits based on the criticality of operations relative to the contamination risk to the product.
- Investigate results that exceed established levels or demonstrate an adverse trend and determine the impact on the sterility assurance of finished drug products intended to be sterile. Develop and execute appropriate corrective actions.

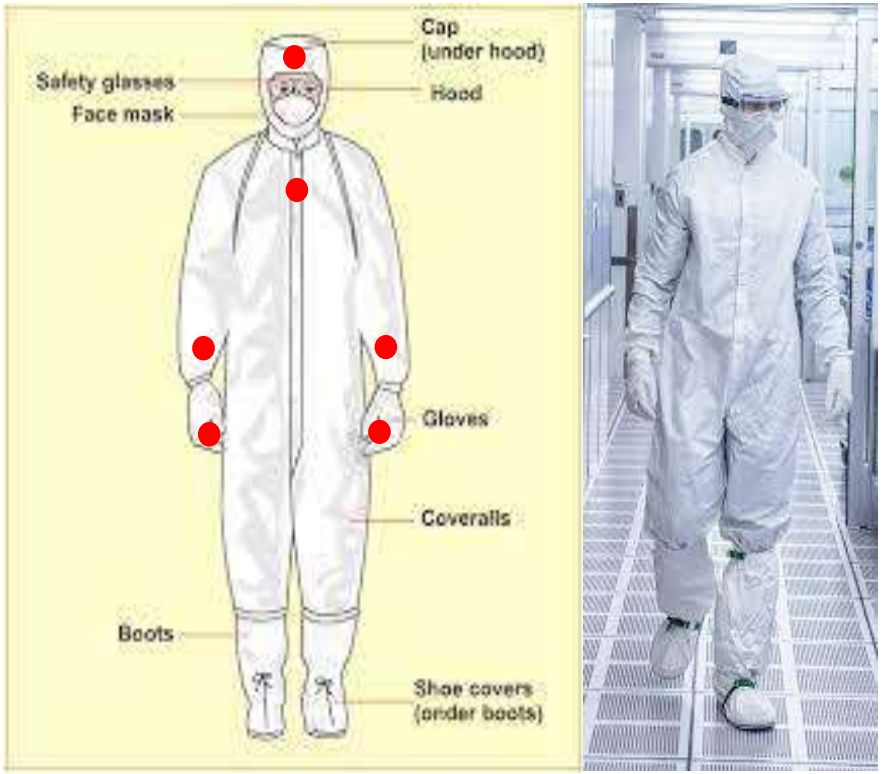
FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Personnel Monitoring Program: Glove Testing for 503A Facilities and Outsourcing Facilities (503B)

- Lack of adequate personnel sampling is considered an insanitary condition.[1]
- Glove testing should be sampled AFTER work in critical area BEFORE sanitizing gloves to assess the actual operating conditions.[2]

[1] FDA Guidance for Industry: Insanitary Conditions at Compounding Facilities. (2020)
[2] FDA Draft GFI titled Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act which, when finalized, will reflect FDA's current thinking on compliance with CGMP requirements for 503B facilities. (2020)

Personnel Monitoring Program: Monitoring Gowns for Outsourcing Facilities (503B)



- Sample site selection should be justified.
- Samples should be collected AFTER work in critical or classified areas and BEFORE sanitizing gown/glove with sterile alcohol.

Challenge Question

True or False: Glove testing should be sample after work in critical area before gloves sanitization?

Media, Incubation, and Reading Environmental and Personnel Monitoring Plates

- Examples of media used for environmental monitoring include Soybean casein digest, SDA, R2A.
- Growth promotion testing (COA; perform testing)
- TSA plates should be incubated at 30-35°C for 2-3 days (TAC).
- SDA plates should be incubated at 20-25°C for 5-7 days (TYM).

- TSA – Trypticase Soy Agar used to recover bacteria, yeast, molds
- SDA – Sabouraud Dextrose Agar used to recover yeast, mold, bacteria
- R2A – low nutrient agar used to recover microbes from potable water
- TAC – Total aerobic bacteria count
- TYM – Total yeasts and molds
- COA – Certificate of Analysis

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

Establish Action and Alert Levels for Viable Particles

Microbiological monitoring levels should be established based on relationship of sampled location to the operation and the need to maintain microbiological control in the facility.

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

a- All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
b- ISO 14644-1 designations provide uniform particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
c- Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
d- The additional use of settling plates is optional.
e- Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

Trending Environmental/Personnel Monitoring Data

- Each individual result should be evaluated for significance by comparison to established action and alert levels.
- Averaging test results may mask unacceptable conditions in localized areas. Remember, microbial contamination is **not** uniformly distributed!
- Data may be trended by location, operator, shift, room, or other parameters.
- Quality Unit should establish procedures detailing the frequency with which data should be reviewed (e.g., daily, weekly, monthly, quarterly, annually). Written procedures should establish how responsible managers are notified of excursions.
- EM and PM data should be evaluated at least annually to determine if there is a need for any changes to manufacturing or facility controls.

FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

483 Observations

OBSERVATION 2

Aseptic processing areas are deficient regarding the systems for environmental monitoring conditions and actionable microbial contamination was present in the ISO 5 area or in adjacent areas during aseptic production without adequate product evaluation and remedial action. Specifically,

A) The gloves for operator (b) (6) were sampled after production in the LAFW on 02/05/19, and the results were above the limit of NMT (b) (4) CFU. The investigation did not include an assessment of microbial quality for the approximately (b) (4) products the operator produced that day and did not identify the microorganism.

B) Operator (b) (6) wore two pair of gloves on 03/04/19 prior to sampling (b) (6) gloved fingertips at the end of production. The operator did not wear two pair of gloves during production on any other day during this inspection, and you stated personnel only wear two pair of gloves for fingertip sampling. The operator produced lot 03042019@10 for intrathecal administration, dispensed 03/04/2019.

C) Your firm did not conduct personnel and surface monitoring every (b) (4) weeks per the approved SOP. There are several examples when your firm did not perform personnel and surface sampling for approximately (b) (4).

Environmental Monitoring: Temperature and Humidity

- 21 CFR 211.46(b) states: “Equipment for adequate control over air **pressure**, microorganisms, dust, **humidity**, and **temperature** shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.”

- 21 CFR 211.42(c)(10)(ii) mentions **temperature** and **humidity** controls are important for aseptic processing.

Environmental Monitoring Program: Differential Pressure

- Maintain equipment for adequate control over air pressure 21 CFR 211.46(b)
- Establish differential pressure limits and (21 CFR 211.42) and control systems should include built-in alarms to detect excursions.
- Positive pressure of 10-15 Pascals (0.04-0.06 inches of water gauge*) should be maintained between rooms of higher and lower air cleanliness with the doors closed.
- If pressure reversals occur during operations that cannot be promptly corrected to prevent contamination during production (aseptic processing), production should stop until a correction is made.

*FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. (2004)

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

Environmental Monitoring Program: Differential Pressure

The failure to detect and adequately address a change in air quality of any classified area before there is a loss of environmental control that may impact drug sterility is an **insanitary condition**. Examples include:

- Inadequate pressure differentials between areas of higher quality air and lower quality air
- No or infrequent measurement of room pressure differentials during operations to demonstrate proper air flow
- Pattern of frequent or acute pressure reversals from areas of less clean air to areas of higher air cleanliness

FDA Guidance for Industry: Insanitary Conditions at Compounding Facilities. (2020)

483 Observations

OBSERVATION 7

Pressure differentials between areas with different air classifications were not monitored prior or during sterile drug production. Specifically, there is no verification of the pressure differentials before or during sterile drug production. Pressure differentials are measured with (b) (4) manometers which are not visible from within the cleanroom. The values are documented (b) (4); no time is recorded.

OBSERVATION 6

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

Specifically,

Your firm is unable to provide documentation of positive pressure monitoring in the clean room during sterile drug production for the time period prior to March, 2018.

Environmental Monitoring Summary: Outsourcing Facilities (503B)

	Outsourcing Facilities (503B)	
What?	**Where?**	**How Often?**
Non-viable particles (air)	Classified rooms (e.g., ISO 5, ISO 7, ISO 8) All ISO 5 areas (e.g., LAFs, BSCs, isolators)	At least daily during production (Cover all production shifts)
Viable particles (air)		
Viable particles (surfaces)		At least daily **after** production[1] (Cover all production shifts)
Personnel monitoring	Glove fingertips and strategic locations on sterile gowns	Glove fingertips every shift; sample gown locations periodically and during gowning qualification
Differential pressure	Between classified areas & between classified and unclassified areas	Continuous monitoring; alarm system to notify when OOS
Temperature	Classified areas and controlled non-classified areas	Continuous monitoring
Relative humidity		

[1] As soon as is possible **after** operations are complete, but BEFORE cleaning and disinfection.

Note: These recommendations are suggested monitoring frequencies for outsourcing facilities that follow CGMP requirement. How **frequently** monitoring should be performed differs for 503A and 503B facilities and should be commensurate with risk to product.

FDA Draft Guidance for Industry: Current Good Manufacturing Practice – Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act. (2020)

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