Centre for Biopharmaceutical Excellence

Microbiology Controls
Environmental Monitoring Programs

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Module Topics

- Fundamental EM Program – what to monitor
- Frequency, Location and Methods
- Monitoring Water Systems
- Managing an EM program for Sterile Cleanrooms

Some Important References

- EU/PICs/TGA cGMP Annex 1 – Sterile Products
- PDA Technical Report #13 Fundamentals of an Environmental Monitoring Program
- USP <1116> Microbiological Evaluation of Cleanrooms
- FDA Guidance – Aseptic Processing
- ISO 14644 Series - Cleanrooms and associated controlled environments

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How Important is Environmental Monitoring ?

- The answer lies in risk assessment
- The GMPs for sterile products has clearly defined GMP rules
- The GMPs for non-sterile products have poorly or un-defined expectations

- How important - depends entirely on:
- the dose form and use of the product
- the types of product manufactured (sterile / non-sterile)
- Whether potent materials are handled in the facility

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Why do we monitor ?

- **Particulates:** Verify that the HVAC systems is functioning correctly and rooms are meeting specifications. Particles are associated with physical contamination and indirectly micro-biological contamination.

- **Microbiological:** The purpose of viable environmental monitoring is to:
  - verify the integrity of the cleanroom air and HVAC systems
  - monitor the effectiveness of surface C&S programs
  - monitor operator performance via personnel monitoring.
  - Monitor aseptic process integrity in Grades A and B

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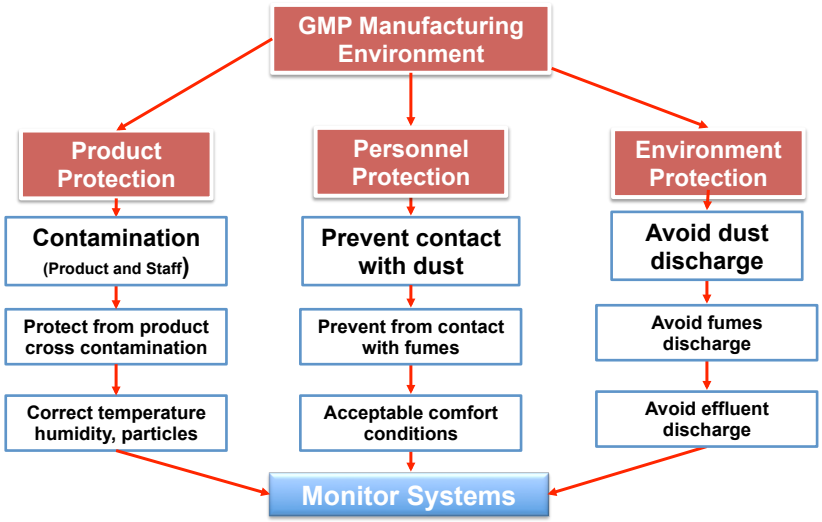
Environmental Control



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What should be monitored ?

Physical

- Particles at rest
- Temperature
- Relative Humidity
- Room Pressures

Biological

- Bacteria
- Yeast and moulds

Pharmaceutical Services

- Water system and in some cases steam
- HVAC
- Pharmaceutical gases

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How Frequently ?

- Is a risk based decision which depends on:
  - the dose form being processed
  - whether the processing is **"closed", "contained"** or **"open"**
- Sterile products / aseptic processing have defined requirements for Grade A, somewhat for Grade B and not defined clearly for Grade C and D
- Non-sterile products – the frequency is not defined in PICs GMPs
- Need enough samples to conduct trending over a year

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What Methods (Biological) ?

Each method has limitations

Suitable **combination** of:

- Settle plates
- Contact (RODAC) Plates
- Surface Swabs
- Active Air Sampler
- Flush Water (from Equipment)
- Endotoxin for some sterile products equipment

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What Sample Locations to Choose ?

- Defined for particulates generally in ISO14644 and cGMP Annex 1
- Risk based decision for micro-biological monitoring
- Microbiological driven by the **purpose of sampling**
- Considerations:
  - Proximity to the product
  - Product contact equipment surfaces
  - Whether testing for cleaning verification or product purity

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Cleanroom cGMP Microbial Limits – Annex 1

Grade	Recommended limits for microbial contamination			
	Air sample cfu/m^3	Settle plates (diam 90mm) cfu/4 hrs	Rodac plates (diam 55mm) cfu/4 hrs	Glove print 5 fingers cfu/glove
A	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

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Example Locations - Sterile

- Examples of common locations are:
  - near open filled containers (air sample)
  - proximal to air return (air sample)
  - floor and door handles (swabs)
  - filling nozzle (post filling swab only)
  - gloved hand (contact plate)
  - obstacles that may create turbulence (air)

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Example Locations – Non - Sterile

- Post processing product contact equipment cleaning surfaces
- Hardest to clean locations for direct product contact surfaces
- Rooms with open processing – more frequent
- Rooms with “contained” processing – lesser frequency
- Rooms with closed processing – less frequency
- Non-processing rooms - infrequent

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Relative Frequency of Monitoring – Rooms for Non-Sterile Facilities

- **Lowest Risk (I) -** low risk rooms – monitor 1 - 2 months
- **Moderate Risk (II)** – medium risk rooms monitor 2 - 4 weeks
- **Higher Risk (III)** – higher risk rooms – monitor weekly

Example Only

Room Activity	Dry Oral Solids	Liquid / Creams
No Product / Materials Exposed	I	I
Processing Equipment Storage	I	II
Packaging Areas	I	II
Open Product Exposed	II	III

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Examples of Non-Sterile Limits

Cleaned Equipment Limits (Swabs)

Microbiological Limits for Surfaces Swabs (post clean)	Alert Levels per Swab (25cm²)	Action Levels per Swab (25cm²)
Surface not in immediate contact with product (e.g. lid)	> 2 cfu/swab Any mould	≥ 5 cfu / swab > 1 mould
Surface in immediate contact with product (e.g. inside tank)	Any positive	≥ 2 cfu / swab Any mould

Example Only

Cleaned Facility Limits (Air Sample)

Alert Limit			Action Limit		
Bacteria	*Yeast Mold*	*Total Count*	*Bacteria*	*Yeast Mold*	*Total Count*
> 25	> 15	> 40	> 50	> 30	> 100

Alert and Action Limits (based on)

- Risk assessment for new production lines
- Historical trends for established process lines
- Compendial and regulatory guidelines - sterile
  - USP General Information Chapter<1116> Microbiological Evaluation of Clean Rooms and Other Controlled Environments
  - EU-GMP Annex I Manufacture of Sterile Medicinal Products
- All monitoring results should be reviewed regularly to detect trends and to confirm the effectiveness of the cleaning and sanitation program
- Generally QA/QC review: monthly, quarterly and as part of annual review program.

Setting Alert and Action Limits (based on historical trends)

- Underlying data is NOT normally distributed so must transform or use “non-parametric” approach
- Options:
  - Convert to Log10 or Log e – this tends to normalise data
  - Rank in order and cut off at say **97.5%** (action) and **90%** (alert)
  - Use cumulative frequency approach
- This is all OK except it is complicated by:
  - Hard to combine the data from different methods
  - Often limited data available
  - Regulatory limits my be below calculated alert and action limits

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Cleanroom Data – setting limits using cumulative frequency

Result (cfu/plate)	% Occurrence	Cumulative % Frequency
0	86	88%
1 (alert)	**4**	**90%**
2	3	93
3	2	95
4 (action)	**2**	**97.5%**
≥ 5	1	100

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The type of bug matters !

- Mold is a problem in any facility – hard to remove.
  - Set mold limits lower than for total bacterial count limits
- Pseudomonas sp. in water systems and liquids and creams areas
- Known objectionable organisms / pathogens

Should occasionally “speciate” the organisms detected and always when there are unusually high numbers or during an investigation.

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How to Report EM results

- **TAMC** = Total Aerobic Microbial Count
- **TYMC** = Total Yeast and Mold Count
- **TAMC** = TYMC + total bacterial count
- Never report “zero” always NOD (No Organsims Detected)
- **TNTC** = To Numerous To Count (generally means > 300 cfu per plate.

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Microbial Test Methods and Their Limitations

- Incubation conditions:
  - Y & M: 20°C - 25°C for 5 days (SAB or TSA plates) and
  - Bacteria: 30°C - 35°C for 3 days – TSA Plates
- Microbiological monitoring test limitations:
  - incubation temperature and time may not be optimal for all organisms
  - Medium/plate used may not support the growth of all organisms
  - disinfectants may inhibit growth
  - sampling procedures, sample handling and transport may affect test results.
- Validate microbiological surface methods for recovery > 70%. Must neutralise inhibitors/disinfectants

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The Paperwork

- Sample Location
- Date sample taken (length of time for settle plates)
- Batch number and expiry of the media
- Operator(s) who took the samples
- State of the room (at rest or in operation and activity)
- Incubation conditions
- Operator reading the plates and date read
- Number of cfu per sample – separate for Yeast / Mold
- Any identification
- Signature of person reviewing the results

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EM Test Method Validation

- Required but limited to % recovery and fertility

EM Settle Plates

- Qualify plates per supplier by recovery study > 70% expected
  - Add say 100 cfu to the plate then count % recovered for a bacteria, a yeast and a mold
- Consider sanitant inhibitor plates
- 4 hour exposure
- Use near expired plates
- Add back specified organisms or alternative
- Problem with water re-constitution

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EM Test Method Validation

- Required but limited to % recovery and fertility

EM Contact Plates

- Qualify plates per supplier by recovery study > 70% expected
  - Add say 100 cfu to three different surfaces then count % recovered for a bacteria, a yeast and a mold
- Consider sanitant inhibitor contact plates
- Use near expired plates

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EM Test Method Validation

- Required but limited to % recovery and fertility

EM Swabs

- Add say 100 cfu to three different surfaces then count % recovered for a bacteria, a yeast and a mold
- Are qualifying each “swabber” technique
- Consider sanitant inhibitor – peptone water

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Particle Counting – Non Sterile

For non-sterile processing areas – Grade D Cleanroom (Higher Risk Locations)

- Periodic particle monitoring of higher risk Grade D cleanrooms is useful in detecting potential breakdown in facility HVAC engineering and deviations from qualified processing norms (e.g., clean area classification).
- A result outside the established classification level at a given location should be investigated as to its cause.
- The Grade D areas are measured in “at rest” conditions only.

For non-sterile processing areas – Other Zones

- No particle monitoring is required for other zones as there is no particulate limit classification. Any testing, if done for qualification purposes should be undertaken in “at rest” conditions only.

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Physical Monitoring

Pressure Differentials

- Generally continuous by a validated BMS or
- Magnehelic gauges outside each processing room read daily
- Generally > 15Pa (sterile) and > 10Pa (non- sterile) differentials
- Verify air flow directions between rooms “at rest”

Temperature / RH %

- Either BMS system or in- room physical monitors
- Record Max and Min per day

Filter Integrity

- Annual clean and test for % penetration
- Velocity not usually measured for non-sterile rooms, except for validation purposes / air change rate calculations.

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Pharmaceutical Water Monitoring

- Feed (Potable) Water
- Purified water
- Highly Purified Water
- Water for Injections – PFW & WFI
- Softened Water
- Water for Final Rinse
- Pure, or clean Steam
- Water for cooling Autoclaves

- Each has a different monitoring requirement

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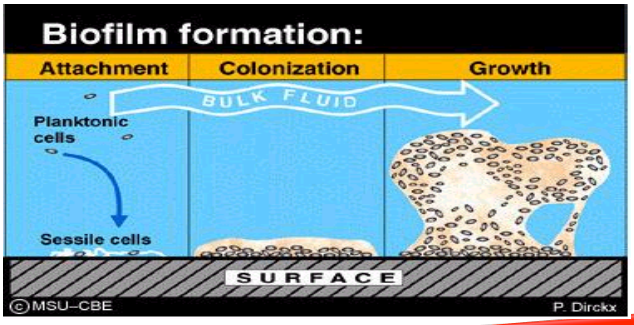
What goes on inside your water system if it's not maintained

- Free swimming aquatic bacteria – mostly G-ve .. .see this as general background bacterial count
- Biofilm build up on surfaces – see this as intermittent spikes
- Key is a good simple design + periodic validated sanitation strategy



General Water EM Rules

- **Purified water** may use pour plate method:
  - Minimum sample size: 1ml
  - Media: PCA or R2A (depending on limits applied)
  - Incubation: 48 - 72 hours at 30-35^{0}C
- **WFI - use membrane filtration**:
  - Minimum sample size: 100ml (use 250mL)
  - Media: R2A agar (low nutrient)
  - Incubation: 48 - 72 hours at 30-35^{0}C
  - Monitor endotoxin levels (< 0.25EU/mL)
- Identify recovered organisms to genus level or for WFI to species level.

Water Sampling

- Must have a water system map – with numbered sampling valves for up stream and points of use (POU)
- Pre-clean outlet with 70% alcohol. (TOC sample last.)
- Use “aseptic” technique – requires and SOP
- Sample through production use hoses and flush prior to sampling
- Store samples in fridge unless testing within 4 hours. Test ASAP (<24 hours)

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Water Standards

- British and European Pharmacopoeia monographs
- United States Pharmacopoeia <1231>
- CPMP/QWP/158/01 – Guidance – Quality of water for pharmaceutical use

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Microbial Limits (USP <1231>

Manufacturers should establish **"alert" and "action" limits** based on the use of the water plus capability of the system. They may involve levels of total microbial counts or recoveries of specific microorganisms

There are certain maximum microbial levels above which action levels should never be established.

Generally considered **maximum action levels** are:

- **100 cfu per mL for *Purified Water***
- ***10 cfu per 100 mL for Water for Injection***
- ***For WFI - LAL < 0.25EU/mL***

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Expected Limits

Purified Water	• Target < 1cfu/mL on average • Alert > 10cfu/mL • Action** >100cfu/mL
WFI	• Target < 1cfu/100mL "effectively sterile" • Alert > 1cfu/100mL/ any LAL count • Action** > 10cfu/100mL / 0.25 EU/mL

** Should set action limits below compendial limits if possible

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Developing and Managing a Cleanroom Microbiological Monitoring Program for Sterile Products

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Who Should Monitor ?

Oversight by QC Microbiology

QC Led Team

- Independent of Production
- Policeman approach
- Not efficient utilisation of resources

Production Led Team

- Pragmatic approach
- In-process control
- Must have strong QC oversight
  - Training of operators
  - QC surveillance program
  - Random audits by QC

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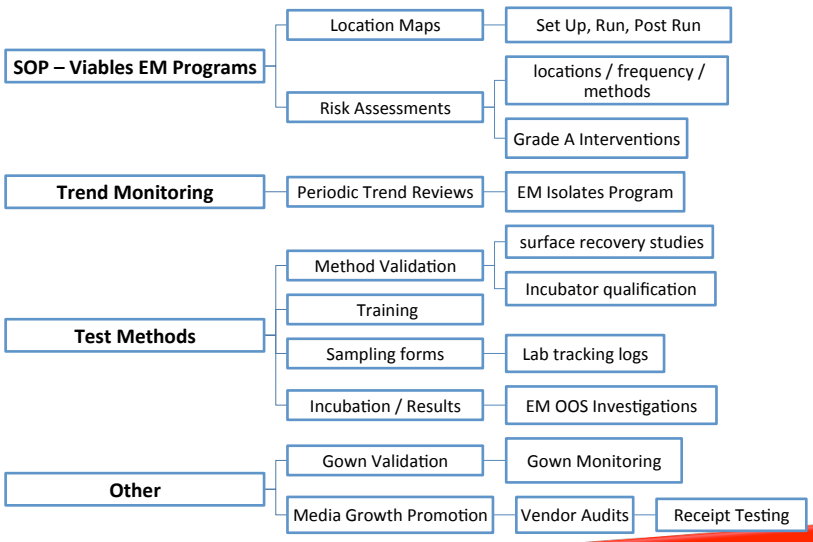
Core EM Documentation



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EM Programs and Sanitation

- EM data monitors the effectiveness of the C&S program
- There is no one magic sanitant so a combination is needed.
  Vegetative cells ➔ Fungal spores ➔ Bacterial spores
  Sanitisers .... Disinfectants ..... Sporicides…....
- EM Trend reviews underpin confidence in C & S program and cleanroom management
- Should identify & trend fungi/mold separately to bacteria
- For new sanitant should validate effectiveness “in field”. Sanitant surface residues can inhibit EM growth

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Establishing a Viables EM Program for Grade A and B

1. Engage Microbiologist and Aseptic Operators
2. Study the fill line, process, critical space and Grade B Rooms
3. Study personnel and materials movement
4. Conduct air visualisation studies “at rest” then in “simulated operation”
5. Characterisation study for extended period (if possible) grid rooms
6. Risk assess worst case locations:
   - Critical space and critical surfaces
   - Areas with high activity or personnel frequently in proximity
   - Areas with high personnel traffic or areas frequently touched
   - Areas difficult to sanitise effectively
7. 3 times OQ at rest after C&S program
8. 3 times PQ in operation after C&S program
9. SOP - Fixed and rotational locations in 1st 12 months – review 3 monthly then update after review.

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Interpreting Industry Limits (Grade A and B Space)

	Active Air cfu per m^3	Passive Air (Settle – 4 hr)	Surface (Rodac/Swab)	Personal (Glove 5 finger)	Personal (Gown)
EU/PICs/Who Annex 1	A < 1 B 10	A < 1 B 5	A < 1 B 5	A < 1 B 5	Not specified
US FDA Class 100 Class 10,000	1 10	1 5	Not specified	Not specified	Not specified
USP <1116> (incident rate)	ISO 5 <1% ISO 7 <5%	Same incident rate as active air	Same incident rate as active air	Same incident rate as active air	Same incident rate as active air
Japan Aseptic Guide (JPXV1)	A < 1 B 10	A < 1 B 5	A < 1 B 5	A < 1 B 5	Not specified

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Interpreting Industry Limits
(Grade C and D Space)

	Active Air cfu per m^3	Passive Air (Settle – 4 hr)	Surface (Rodac/Swab)	Personal (Glove 5 finger)	Personal (Gown)
EU/PICs/Who Annex 1	C 100 D 200	C 50 D 100	C 25 D 50	Not specified	Not specified
US FDA Class 100,000	100	50	Not specified	Not specified	Not specified
USP <1116> (incident rate)	ISO 8 <10%	Same incident rate as active air	Same incident rate as active air	Same incident rate as active air	Same incident rate as active air
Japan Aseptic Guide (JPXV1)	C 100 D 200	C 50 D 100	C 25 D 50	Not specified	Not specified

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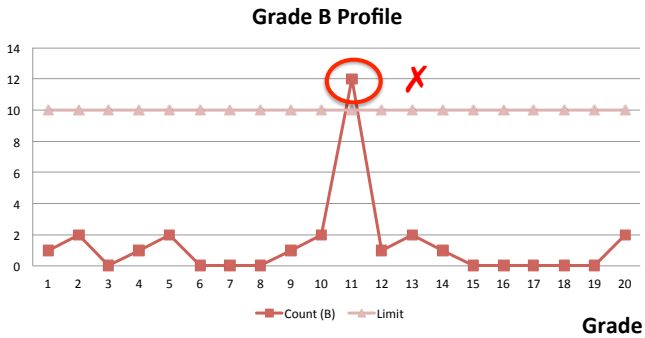

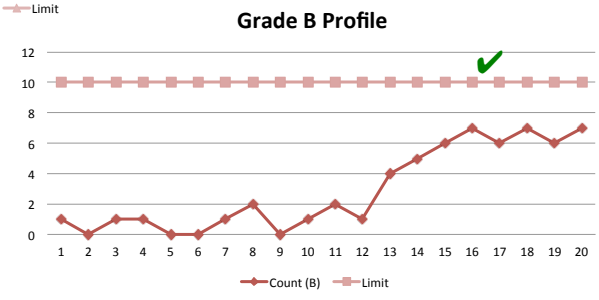

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Minefields in Limit Interpretation

- Numbers matter but trend changes matter as much
- PICs says “on average” but single excursions matter
- Based on total counts but species matter e.g yeast/mold, pseudomads …..
- Limits have caveats regarding methods / conditions
- Grades B, C and D limits are generally excessive in a well controlled cleanroom
- These are regulatory or “action” limits – companies expected to develop “alert” levels
- USP <1116> proposes incident rates instead of numbers – basis is trend monitoring.
- Significance is related to the proximity to open product

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Example Setting Action and Alert Levels Using Ranking

cfu count	Rank	Percent	
59	1	100.0%	
33	2	97.9%	Action @ 95%
22	3	95.9%	
18	4	93.8%	Alert @ 90%
18	5	91.8%	
18	6	89.7%	
17	7	87.7%	
16	8	85.7%	
14	9	83.6%	
12	10	81.6%	
11	11	79.5%	
11	12	77.5%	
10	13	75.5%	
10	14	73.4%	
10	15	71.4%	
etc ….	etc …..		

Range of approaches used but need to set alert / action limits scientifically;

Ranking cut off is only one approach;

Must have sufficient data available;

Action Limit ≤ Regulatory limit;

Exceeding alert limit is not grounds for corrective action;

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Example Alert and Action Responses

If ……	Then ….. also refer to SOP xxxx
Any result exceeds the alert limit (or there is a trend)	• Identify the organism to genus level • Inspect the cleaning record for the equipment to verify it was properly cleaned and sanitized • Notify the QC Manager of the result • Initiate Alert Report (F xxxx) to notify the QA Manager and Production Manager
Any result exceeds the action limit	• Identify the organism to species level • Inspect the cleaning record for the equipment to verify it was properly cleaned and sanitized • Review the testing trends for all equipment used in non-sterile production • Notify the QA Manager of the result – determine whether a product risk assessment is warranted, or not. • Test the product for the absence of the identified organism • Initiate Deviation Report (F xxx) to notify the QA Manager and Production Manager

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What methods are suitable?

Each method has limitations and advantages so needed in combination.

Suitable **combination** of:

- **Settle plates** – passive limited space but extended time coverage
- **Contact (RODAC) Plates** – small flat surface areas
- **Surface Swabs** – larger inaccessible areas but harder to recover
- **Active Air Sampler** – better detection but limited time duration
- **Gloves and garments monitoring** – hit or miss.

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What Sample Locations to Choose ?

- Defined for particulates generally in ISO14644 and cGMPs
- Risk based decision for micro-biological monitoring
- Microbiological driven by the **purpose of sampling**
- Considerations:
  - Proximity to the product
  - Product contact equipment surfaces
  - Whether testing for cleaning verification or product purity

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Site Selection Considerations

- Can use a combination of grid mapping by room and risk assessment by location in room
  - Sites or process steps where contamination may adversely effect product
  - Sites likely to accumulate microbial load during processing or use
  - Potential “dead spots” in room
  - Sites most difficult to clean or sanitise
  - Means of microbial dispersion in the room environment via:
    - People, equipment, processes, materials and air flows
- Must also consider risk to product associated with the sampling itself
- Must be able to remove any media residue from surfaces
- Must not interfere with operators during processing

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Grade A
Critical Space and Critical Surfaces

Critical Space – Grade A / ISO 5

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility.

Critical Surfaces within Critical Space

Not all Grade A space is a critical surface.

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 processing. Generally monitored post processing.

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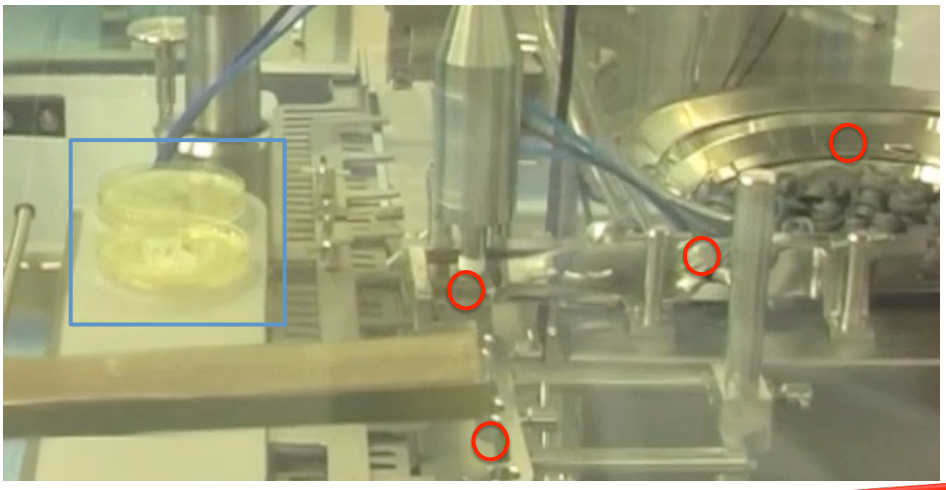
Critical Space and Critical Surfaces



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Example Locations – Sterile Suites

Grade A Space

- Generally only at or above working height
- Near open filled containers (air sample)
- Critical surfaces (post filling swab only)
- Obstacles that may create turbulence (air)
- Curtains and machine doors
- Beneath equipment / floor ?
- Post changeover of lines

Grade B Space

- Proximal to air returns
- Door handles (swabs)
- Obstacles that may create turbulence (air)
- Trolleys
- HMI Consoles
- Floor / Walls/Windows
- Pass throughs
- Adjustment tools

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Example Locations – Grades C and D

- Post processing product contact equipment cleaning surfaces
- Hardest to clean locations for direct product contact surfaces
- Rooms with open processing – more frequent
- Rooms with “contained” processing – lesser frequency
- Rooms with closed processing – less frequency
- Non-processing rooms – infrequent
- Air locks
- Drains, washbays ?

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Personnel Monitoring Aseptic Operators

Sterile Gowns

- Initial qualification 3 times per operator
- 6 or 12 monthly gowning verification
- End of day surveillance - operators in rotation
- Multiple spots in rotation

Gloves

- Initial qualification
- End of aseptic session / end of shift in rotation
- Post entry into Grade A space for all “high risk” interventions
- Left and right hands – 5 fingers

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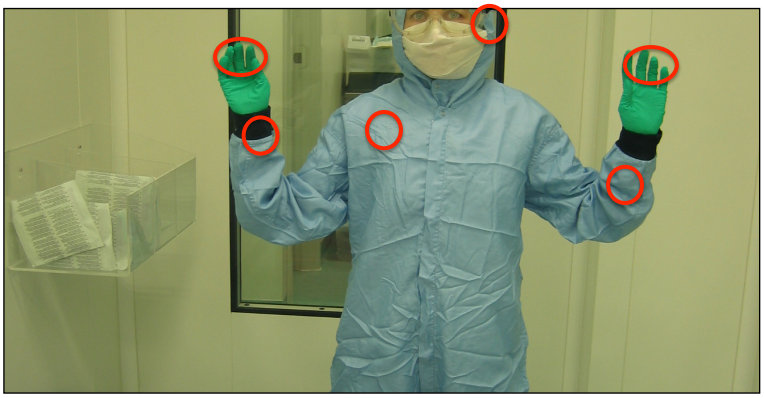
Gown and Glove Monitoring with Rodacs



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How Frequently to Monitor ?

- Is a risk based decision which depends on:
  - the dose form being processed (aseptic / terminal)
  - whether the processing is **"closed", "contained"** or **"open"**
- Sterile products / aseptic processing have defined requirements for Grade A, somewhat for Grade B.
- Grade A and B expect some frequent/continuous coverage – settle plate exposure enable this
- Not defined for Grade C and D. Need enough samples to conduct trending over a year – minimum monthly
- Some fixed locations and some rotational

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Example of Good EM Annual Review

Grade	Type of Monitoring	Filling Room # 1	Filling Room # 1 Vial Storage	Filling Room # 2
A	Active Air	561	187	19
	Passive Air	561	187	19
	Surface	1587	0	56
	Total EM Samples	2659	374	94
	Number Positives	0	0	0
B	Active Air	561		38
	Passive Air	0		19
	Surface	2171		220
	Total EM Samples	2732		277
	Number Positives	0		0

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EM Excursions and Product Quality

- *"Alert and action limits do not define product attributes such as sterility and therefore should not be considered as product specifications or extensions of the product specification."*
- *"Rather they are intended to indicate changes so that corrective action may be taken before product quality is adversely affected."*
- *"Investigations are expected for action level excursions or adverse trends." (Using a written investigation plan)*

PDA TR 13 EM Fundamentals 2014

Grade A / B Excursions and Investigations

- Sample type - contact plate, settle plate, active air sampler, gown)
- Location of sample (distance to critical surfaces)
- Review of relevant air visualisation / smoke studies
- Microbiogical identity to species level
- Review of operations during time period (include operator interview, video review, review of event logs)
- Review of relevant EM data (micro, physical - differential pressure, non viables, temp, humidity)
- Review of trend data (historical and after the event)
- Further investigations in regard of potential sample contamination either during sampling or in the labs
- Specific monitoring programs to support root cause investigations

Crucial information for EM Excursion Risk Assessments

- Is it an isolated event (only 1 sample contaminated)?
- Quantity of contamination (e.g 1 CFU or 25 CFU)
- What is the type of organism ?
- Identification of microorganism (human origin, mold, etc.)
- Plausible most probable root cause(s) informs assessment of product exposure or impact
- Distance to open product and/or critical surface (including airflow pattern)

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Usual suspects - sources of organisms

- Personnel ! Operators, cleaners, fitters, transients
- Personnel ! Poor gowning practices
- Personnel ! Poor aseptic techniques / hand sanitisation
- Tracked in via ancillary equipment – trolleys, tanks etc.
- Poor aseptic transfers of materials through pass through etc.
- Inadequate cleaning eg. underneath equipment or on conveyors
- Via leaks in HVAC / HEPA system

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Case Example # 1

- Single Grade A organism – *Bacillus. subtilis*
- Contact plate post filling
- Detected on guard rail for vials near filling station
- Track record of line is good
  - No sterility failures
  - No media fill fails
  - Excellent history of EMs in last 2 years
  - Operators are qualified and well trained

Investigation

- Source
- Fate of the batch
- Corrective Action(s)

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Other examples – Grade A Excursions

1. Active air sampler + settle plate, filling area during filling – 1 mold + 1 mold = reject
2. Left glove, set up stopper hopper, below product contact surfaces – 1 bacteria (*Staph. epidermidis*) = release
3. Filling needle post fill swab – 1cfu *Staph. aureas* = reject
4. Left glove, freeze dryer loading using RABS technology, operator well separated from semi stoppered vials – 3 cfu (2 x *Corynebacterium afermentans, Kocuria varians*) = release

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In summary

- EM is expensive and outcomes can be problematic
- Must pay attention to the small details
- No direct relationship to product quality – degrees of separation is important
- Risk assessment and trend monitoring are fundamental elements
- The more distance between personnel and critical space / surfaces the better …. case for RABS and Isolator technology.

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