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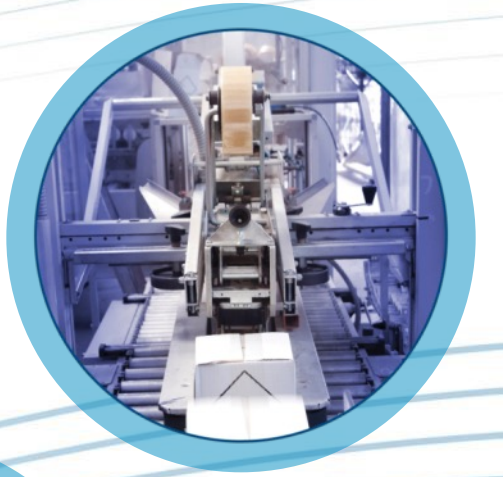
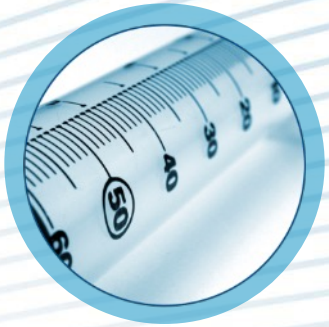
Important Aspects in Environmental Monitoring





By Guenther Gapp

15 September 2023

Agenda

11:00 **Important Aspects in Environmental Monitoring**

- TR 13 Fundamentals of an Environmental Monitoring Program
- Regulatory Requirements and Expectations
- Rationale for Sample Locations and Frequency
- How to Proceed in Case of Excursions

VR Simulator - Session: Understanding Human Errors and Gaining Hands-On Experience

Overview about Presentation

- Introduction: Why is EM (= Environmental Monitoring) required and what does it mean ?
- References (PDA TR 13/ Annex 1/ FDA)
- Rationale of EM Sampling Locations
- Action & Alert Levels / Limits/ Requirements
- “My Best Practices”
- Microbiological Laboratory – points to consider
- How to execute Trend Analyses / Historically Based Alert Levels

What is EM ?

Control, that environment of open product/ open containers / Critical surfaces are not contaminated

- EM is related **to Clean Rooms** (including isolators) / **Water**/ Process Air/ Nitrogen/ ...

- EM is an Indirect Control and Monitoring of product quality , and no direct quality parameter (no specification as Sterility, Endotoxins/ ...)

Which methods are used ? Elements of Environmental Monitoring (Clean Rooms)

- Viable air monitoring (Active and Passive)
- Total airborne particulate monitoring
- Surface monitoring
- Personnel monitoring
- Temperature and relative humidity monitoring
- Room air pressure differential monitoring

Is a control of ….

- **Viable air monitoring (Active and Passive**) : HVAC control / material and operators particulates (and microorganisms) shedding/ airflow conditions …
- **Total airborne particulate monitoring**: HVAC control/ airflow conditions/ Nonviable and viable particulates
- **Surface monitoring:** Cleaning & Disinfection control, personnel behaviors
- **Personnel monitoring**: aseptic practices/ training
- **Temperature and relative humidity monitoring** (to control acceptable working conditions and product)
- **Room air pressure differential monitoring :** prevent ingress from outside

Important References

- CFR 21 PART 870.70 „Production and process controls“ and 203.32
- PDA Technical Report 13 (2022) / Fundamentals of Environmental Monitoring
- FDA Guidance (Sterile Drug Products Produced by Aseptic Processing/ 2004)
- Eudralex Annex 1 (2022)
- USP <1116>
- PDA Points to Consider Aseptic I and II (2015/2016)

PDA TR 13 (New Release 2022)

Fundamentals of an Environmental Monitoring Program

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PDA TR 13

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PDA TR 13 : Sample Locations Rationale

5.2 EM Sample Site Selection Using Risk Management Principles

Sample site selection, selection of the appropriate sampling methods, sampling volumes, and monitoring frequencies are critical components of contamination control within a facility. However, EM risk assessments are only intended to define the EM program as a part of the overall contamination control strategy. This section addresses how to create and how to maintain an EM program applying a lifecycle approach (**Section 5.2.1**) and the use of quality risk management principles to identify and select sites for EM of classified environments including ISO 5-8/Grades A-D as well as personnel monitoring (**Section 5.2.2**). **Sections 6.8** and **6.9** discuss utilities (WFI/Compressed Air, Nitrogen, etc.).

Suitable sample sites will depend on the area design and manufacturing process. Locations posing the most critical microbiological risk to the product are a key part of the program.

The following factors should be considered when the team is performing the walk-through of the facility:

1. Adherence to industry and regulatory guidelines, e.g., CFR, ISO 14644, USP, FDA, EU (**Note:** ISO 14644 only provides a guidance for the classification of cleanrooms, e.g., minimum number of sample locations for total particulates)

2. Sites and locations where microbial and particulate contamination would most likely have an adverse effect on product quality and, therefore, have the highest risk, considering—

PDA TR 13 : Sample Locations Rationale

- Proximity to open product or product contact surfaces and critical sites (e.g., filling needles, stopper bowls)
- Activities linked with interventions
- Areas that are the most inaccessible or difficult areas to clean and disinfect
- Locations with a high frequency and/or complexity of activities by cleanroom operators, (e.g., touch panel, forceps, door handles)
- Areas with a large number of personnel and high personnel flow (e.g., floors at the entrance of gowning rooms)
- Areas with high material flow

3. Uniform geometric pattern or grid-profiling within the cleanrooms, to cover the complete area
4. Assessment and a justification for locations that will not be part of the EM program due to certain restrictions or alternative/worst-case coverage
5. Historical data and/or data obtained during qualification
6. Anaerobic organisms:
   - Strict anaerobic strains are unlikely to be recovered in common aerobic cleanroom environments. Periodic and/or investigational monitoring for anaerobic organisms may be conducted as a risk-based activity; it is mainly performed to detect any micro-aerophilic bacteria, such as *Cutibacterium* (formerly *Propionibacterium*) *acnes* that usually are not detectable applying standard aerobic monitoring conditions.
   - Generally, a flush or overlay with nitrogen or carbon dioxide does not deplete or replace enough oxygen to create anaerobic conditions that require routine anaerobic-viable monitoring of the area; however, periodic testing of the compressed gasses utilized must be considered.***(11,14,15)***
   - The frequency of anaerobic testing may differ from the routine monitoring schedule. Although anaerobes are a significant component of the skin microbiota, aerobic environmental monitoring is considered adequate to detect inadequate gowning and poor aseptic technique by cleanroom personnel. Anaerobic environmental monitoring in response to a sterility test failure implicating strict anaerobes should be considered.
7. Airflow visualization studies, that is, smoke studies; areas of concern, such as turbulences and eddies, may be addressed through airflow, process, or facility redesign.

PDA TR 13 : Example about EM Risk Analysis

10.0 Appendix 2: Risk Assessment Examples

Table 10.0-1 shows a real-life example provided by Gapp Associates of a review of an existing EM program at a closed RABS filling operation (vial filling; Grade B background). Note that only 5 risk items - from a total of 19 - are listed in the table below.

Table 10.0-1 Example: Failure Mode and Effects Analysis (FMEA)

Risk Item	Problem Statement / Requirement	Risk Description / Potential Failure Mode and Impact	Causes of process/ product failure	Current Controls and Preventive Actions/ Comments SEV: assess the risk and impact on sterility and regulatory compliance, in case of a deviation/ deficiency to this statement/ requirement OCC: assess the probability, that the related locations and areas are - in fact- microbiologically contaminated DET: assess the probability, that the implemented EM sampling plan/ frequency/ number of samples/ methods would detect - in fact- a potential contamination	SEV	OCC	DET	RPN	Risk Class	Risk Accepted	Mitigation Measures/ CAPAs
1	"High-risk areas" in Grade A are monitored: samples are selected which are: • in close proximity to open product and critical surfaces • linked with an increased number of activities and interventions • linked with an extended time of critical interventions • linked with material flow into Grade A. These areas must be properly monitored and sampled in the EM program.	Potential contamination is not detected in high-risk areas, which results in product contamination in Grade A.	Ingress of particles and microbiological contamination into the high-risk areas by many activities and interventions/ extended activities/ material flow.	The high-risk areas in the RABS are a) the filling and stoppering area b) the stopper bowl and c) the turntable, where depyrogenated, open vials are exposed for an extended time. The above areas are well addressed by the surface monitoring program, but not by an active air monitoring/ surface monitoring at the stopper bowl. A settle plate is exposed. This is a deficiency, since high-risk interventions and aseptic activities are performed in the vicinity of the stopper bowl. (**Note:** active air monitoring is done during the set-up and once in a shift). **SEV: 3** (high impact on product sterility, in case that indirect product contact surfaces = stopper bowl is contaminated) **OCC: 2** (there are several interventions performed, therefore there is a moderate risk) **DET: 2** (no active air monitoring, linked with interventions, therefore reduced detectability and moderate risk; no surface monitoring of critical surfaces, which is a regulatory requirement)	3	2	2	12	MAJOR	N	Introduce an active air monitoring location and surface monitoring at the stopper bowl.

Rationale and Selection of meaningful Samples (my concept > 10 years)

- Following Factors to consider for the selection of meaningful locations/ areas
  - Locations close to open product, or close to product contact surfaces
  - Locations which are product contact surfaces/ indirect product surfaces
  - Locations with a lot of activities by the cleanroom operators, frequently passed /touched locations
  - Sampling locations should represent "worst case positions" e.g.,
    - Floors in grade B, chairs, benches in gowning rooms, door knobs, touchscreens
    - Sampling locations most likely having heaviest microbial proliferation, e.g drains
    - Sites that represent the most inaccessible or difficult to clean and sanitize location
    - Locations with extended storage times of product and product contact surfaces
    - Air exit locations
- Personnel Monitoring: gloves (= fingertips) and forearms of gloves of the cleanroom operators after critical interventions and at exit
- Locations where smoke studies show turbulences or stagnant air
- Important: Active Air Monitoring devices & settle plates:„at working level"

Additional Criteria for Selection of EM locations (my concept > 10 years)

- Areas / rooms with higher temperatures (reason: may support microorganism proliferation/ increase operators perspiration/ wet gowning and furthermore increased shedding of particulates
- Wet areas (water based environments in the vicinity of sinks, drains)
- Extended duration of activities (additionally to the item above “a lot of activities”)
- Low cleaning / disinfection frequency - inclusion of mobile equipment (e.g., trolleys/ mobile vessels)
- EM program may be assessed by a Risk Assessment (FMEA) …. SEVERITY/ OCCURANCE / DETECTABILITY ... Refer to TR 13 example

- Oversight expected about EM in case of „self-controls“ by Poduction

Microbiological Requirements of Cleanrooms / FDA 2004 / Action Levels

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

Comments: .....

Levels/ Definition of Action Level .... / No gloves
„1 cfu“ would be accepted

Microbiological Requirements of Cleanrooms / EU 2008/ Action Limits

	Recommended limits for microbial contamination (a)			
Grade	air sample cfu/m^3	settle plates (diameter 90 mm) cfu/4 hours (b)	contact plates (diameter 55 mm) cfu/plate	glove print 5 fingers cfu/glove
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes
(a) These are average values.
(b) Individual settle plates may be exposed for less than 4 hours.

Comments: limits / average values ... interpretation by industry as a requirement of 0 cfu
Current industry standard: within grade A / Iso 5 ... requirement „0“

Table 2: Maximum permitted microbial contamination level during qualification

Grade	Air sample CFU/m^3	Settle plates (diameter 90 mm) CFU/4 hours [(a)]	Contact plates (diameter 55 mm) CFU/plate
A	No growth		
B	10	5	5
C	100	50	25
D	200	100	50

(a) Settle plates should be exposed for the duration of operations and changed as required after a maximum of 4 hours. Exposure time should be based on recovery studies and should not allow desiccation of the media used.

Note 1: All methods indicated for a specific grade in the table should be used for qualifying the area of that specific grade. If one of the methods tabulated is not used, or alternative methods are used, the approach taken should be appropriately justified.

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

Note 3: For the qualification of personnel gowning, the limits given for contact plates and glove prints in Table 6 should apply.

Note 4: Sampling methods should not pose a risk of contamination to the manufacturing operations.

Table 6: Maximum action limits for viable particle contamination

Grade	Air sample CFU /m^3	Settle plates (diam. 90 mm) CFU /4 hours[(a)]	Contact plates (diam. 55mm), CFU / plate[(b)]	Glove print, Including 5 fingers on both hands CFU / glove
A	No growth[(c)]			
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

[(a)] - Settle plates should be exposed in grade A and B areas for the duration of operations (including equipment set-up) and changed as required after a maximum of 4 hours (exposure time should be based on validation including recovery studies and it should not have any negative effect on the suitability of the media used).

- For grade C and D areas, exposure time (with a maximum of 4 hours) and frequency should be based on QRM.

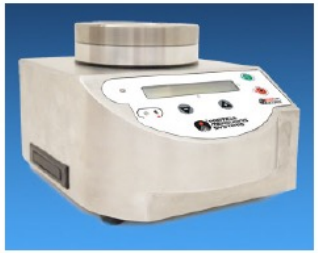
- Individual settle plates may be exposed for less than 4 hours.

[(b)] Contact plate limits apply to equipment, room and gown surfaces within the grade A and grade B areas. Routine gown monitoring is not normally required for grade C and D areas, depending on their function.

[(c)] It should be noted that for grade A, any growth should result in an investigation.

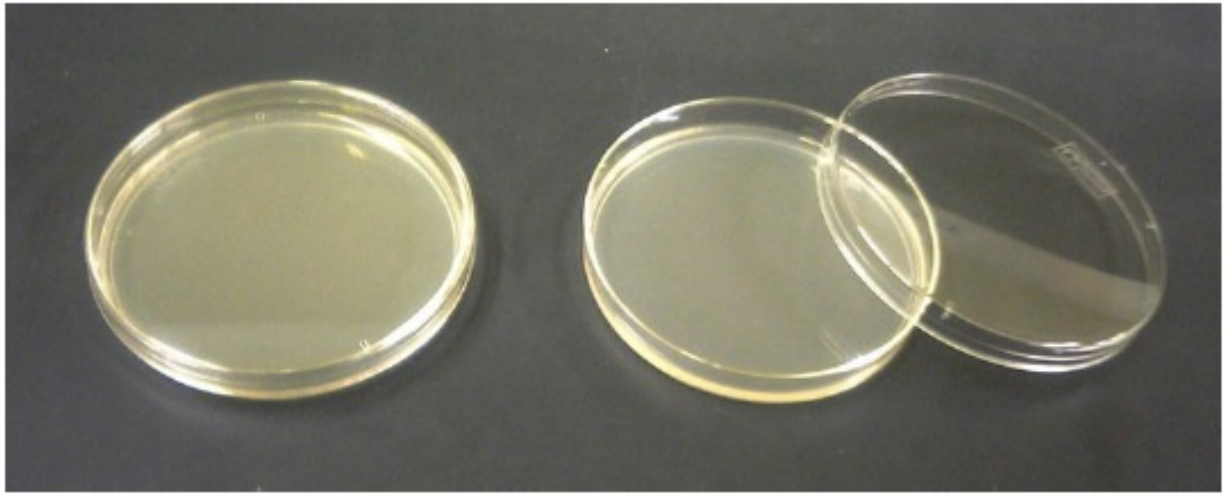
Environmental Monitoring

Viable Air Monitoring



Note: better are „in built systems“ , than the above portable devices

Microbiology Test Methods: Settle Plates



Surface Monitoring

Lower Recovery

?

Swabs

- Employed for equipment and irregular surfaces
- Sample area is usually 25 cm^2

- Contact plates (Rodacs) / 25 cm^2

Nutrient residues

EU Annex 1: some items

9.27 Where monitoring is routinely performed by manufacturing personnel, this should be subject to regular oversight by the quality unit (refer also to paragraph 8.19).

9.25 A risk assessment should evaluate the locations, type and frequency of personnel monitoring based on the activities performed and the proximity to critical zones. Monitoring should include sampling of personnel at periodic intervals during the process. Sampling of personnel should be performed in such a way that it will not compromise the process. Particular consideration should be given to monitoring personnel following involvement in critical interventions (at a minimum gloves, but may require monitoring of areas of gown as applicable to the process) and on each exit from the grade B cleanroom (gloves and gown). Where monitoring of gloves is performed after critical interventions, the outer gloves should be replaced prior to continuation of activity. Where monitoring of gowns is required after critical interventions, the gown should be replaced before further activity in the cleanroom.

9.29 Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. Supporting data for the recovery efficiency of the sampling methods chosen should be available.

Video Surface Monitoring/ Wall

Glove Monitoring: an example

TR 13 Rapid Methods

EU Annex 1: Rapid Methods for consideration

- Tabe 2 and 6:

Note 2: Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

9.28 The adoption of suitable alternative monitoring systems such as rapid methods should be considered by manufacturers in order to expedite the detection of microbiological contamination issues and to reduce the risk to product. These rapid and automated microbial monitoring methods may be adopted after validation has demonstrated their equivalency or superiority to the established methods.

Current Best Practices in Microbiological EM I

- Dynamic Monitoring (DURING) Routine Aseptic Operations (Air Monitoring) / 1 -3 times a 1 m^3
- Settle plates: continuous exposure; alternating; maximum 4 hours
- Set- Up of Filling line (risky) included in EM program
- Surface and Personnel Monitoring: at the end or at the exit, or even after operations ; cleaning afterwards or glove- removal
- Glove Monitoring after Set- up and after “risky“ interventions
- Have a written rationale for Sampling Locations (e.g. worst case locations, see also below) and for number of samples
- Frequency
    - Grade A : shift-wise
    - Grade B: daily
    - Grade C: weekly/ monthly (depends on operation)
    - Grade D: monthly/ quarterly (depends on operation)

Current Best Practices in Microbiological EM II

- Prevent contamination of sterile products by EM execution
- Training /Qualification of EM sampling personnel (by QC or Production)
- QA oversight during EM is very important (Surveillance Monitoring if Production performs EM is recommended)
- Valid growth conditions & prevent secondary contamination
- Good documentation practices (Data Integrity)
- Good Deviations Procedures according to adequate Action / Alert Level requirements
- How to set historically based Alert Levels
- Good Trending Methods

SOP´s : add pictures for detailed location, and rationale for choosing this location

ISM26	To determine effectiveness of cleaning and decontamination process for difficult to clean areas. Site, which if contaminated has adverse effect on product sterility.

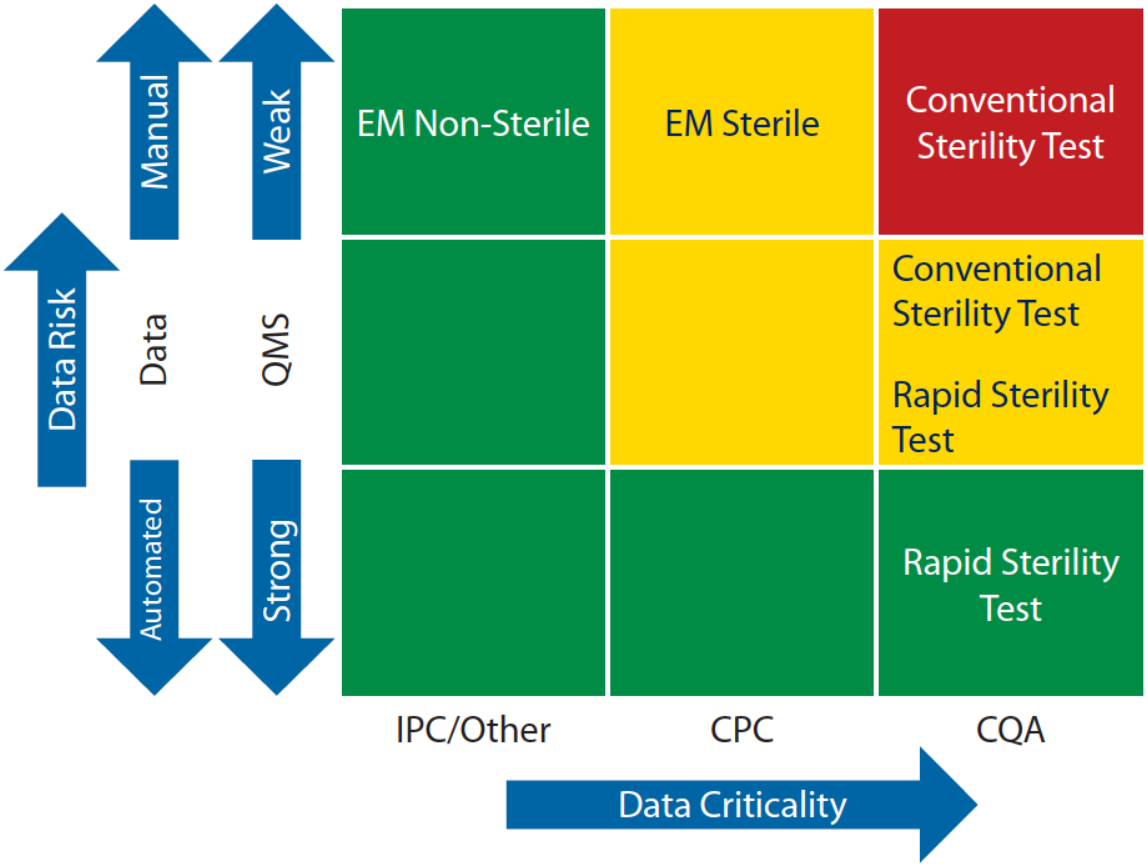
Microbiological Lab: Best practices

- Growth Promotion Testing (of each nutrient batch) , including house- isolates
- One nutrient should be enough (TSA)
- Evaluate elevated temperatures incubation : recovery of molds ?
- For grade A : usage of purchased, gamma irradiated nutrients
- Inactivator is added (of disinfectants or antibiotics)
- Incubation temperatures: should be able to recover molds (split or separate)
- Negative controls in incubator
- Incubator temperature control monitoring / Alarm Management/ Cleaning and disinfection
- Validated Identification methods of isolates (All isolates from grade A should be identified to species level, and a representative number of lower classes)
- Good Documentation practices – independent review by a second person
- Good investigational procedures in case of OOL (out of Level) deviations

Currently, a high percentage of the tests conducted in microbiology laboratories are observational, that is, the results (such as a colony count) are viewed and manually recorded on a paper document or in a computer record. Absent an easy, reliable method to verify the recorded data, some laboratories require microbiologists to use second-person verification (e.g., supervisor) by physical examination of the test plates. Further, the second-person verification could be performed as a discreet step prior to approval of the data or combined with the data-approval step.

Second review verification required,
...if no reliable method to verify recorded data

Potential Data Integrity Risk Matrix for Microbiological Testing

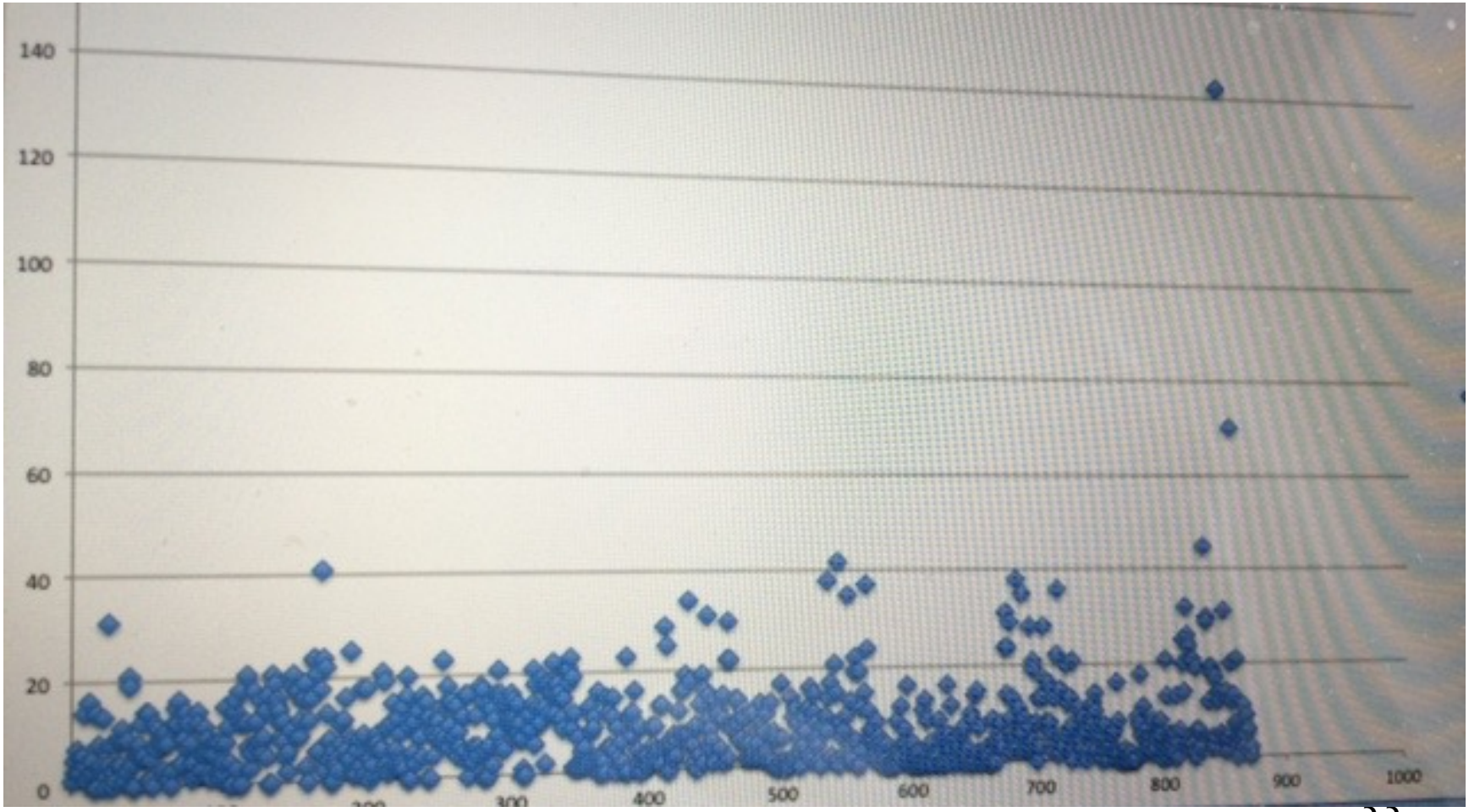


Legend	
CQA	Critical Quality Attribute
CPC	Critical Process Control
IPC/ Other	In-Process Control
Auto/ Elec	Automated/ Electronic
QMS	Quality Management System

Figure 7.2-1 Risk Matrix Example for Microbiological Testing

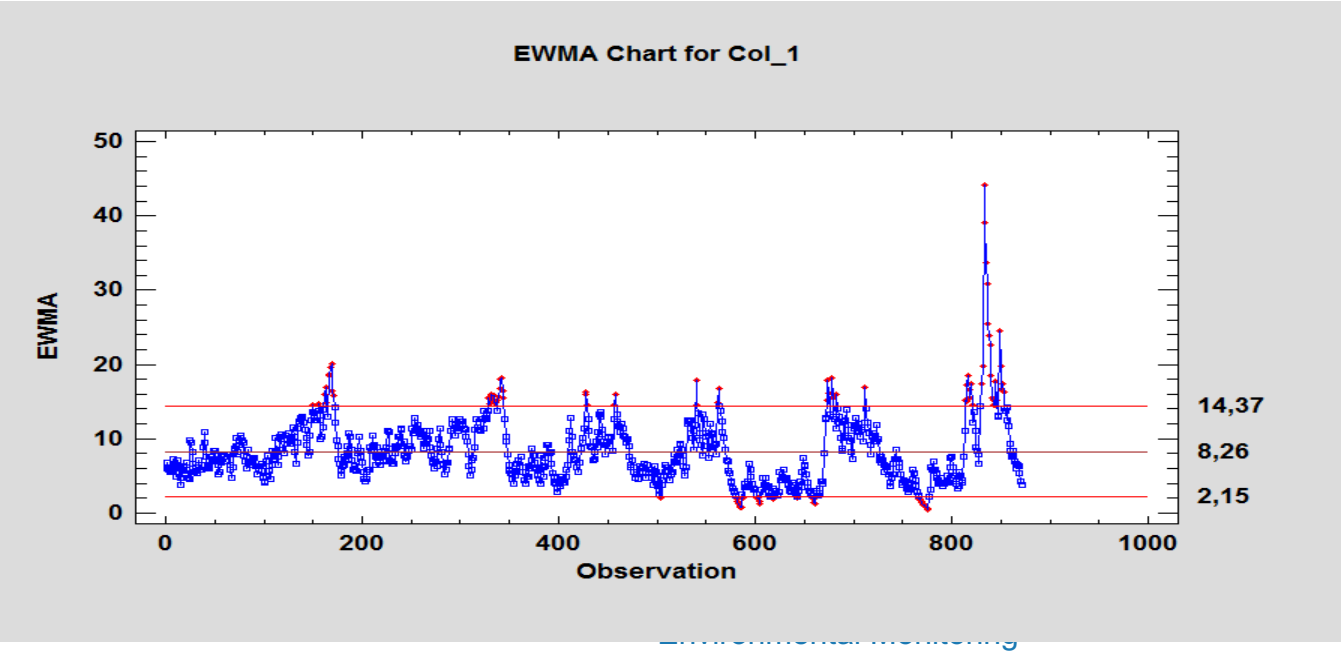
Technical Report No. 80

Trend Analysis: This is no Trend Analysis



Trend Analysis: Points to consider

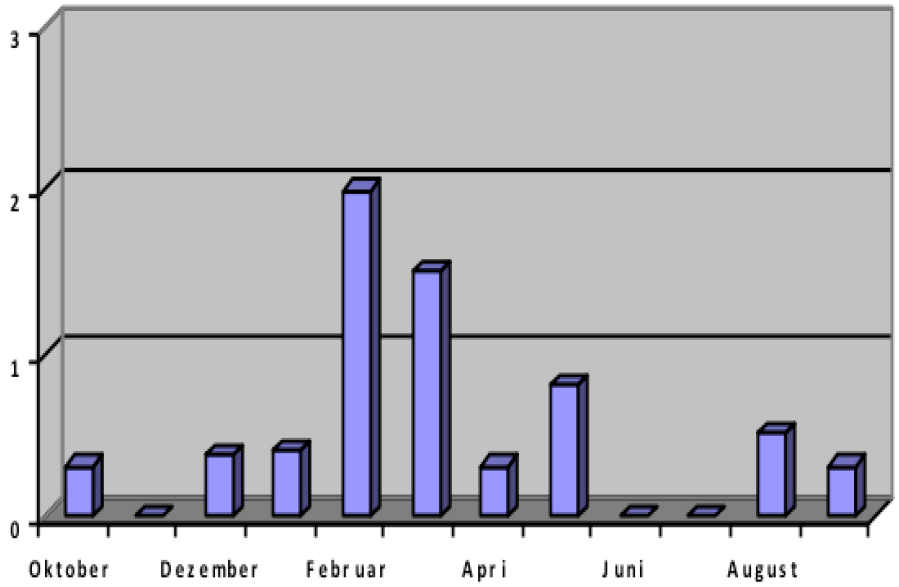
- Historically based Alert Levels: between „95th- 99th Percentile“
- Shifts in trends should be detectable in the graphics
- Recommend to perform this Quarterly and Annually; Written Report
- How to assess „adverse trends“ ? Usage of Statistical Control Charts – use an applicable tool, e.g. „Moving Average analysis“



EM Trending – Quarterly reports

Positive Recovery Results

in Class B (surfaces):

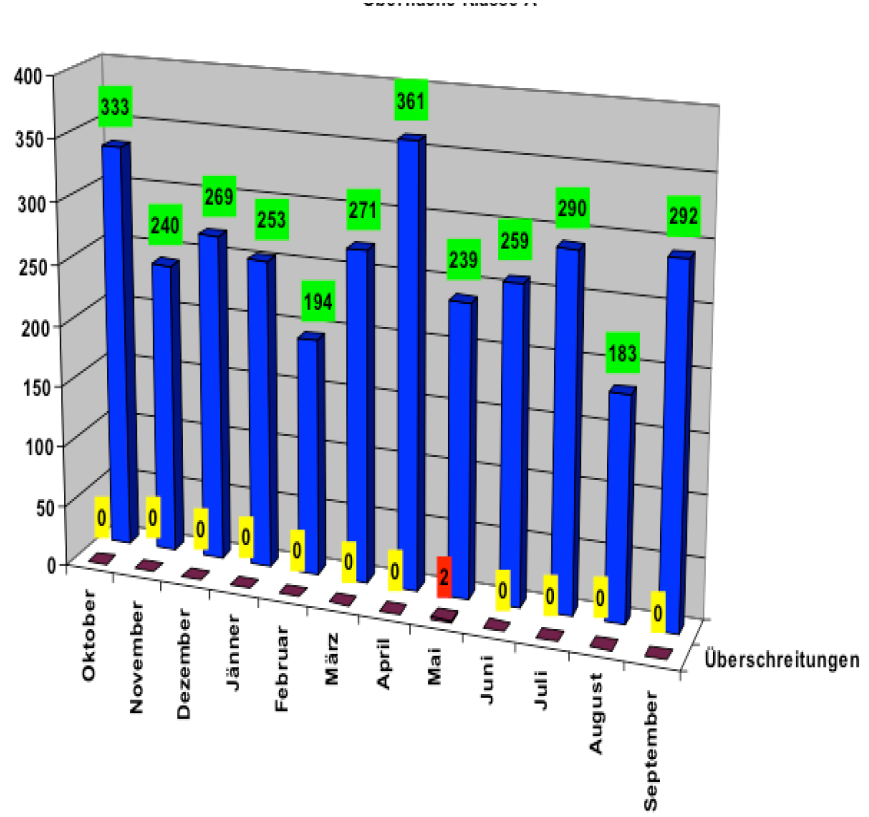


EM Trending – Quarterly reports – Feedback to Personnel

Number samples

OOL results

Illustrate in production area !



What initiates an Investigation ? (my previous rules)

- Action Limit is exceeded
- Alert Level was exceeded for 2 or 3 times
- Trend worsening
- Recovery of objectionable (pathogenic) microorganisms
- Recovery of bacterial „spore-formers“ in Grade A/B
- Higher Percentage of molds detection in the cleanrooms grade C/D
- Missing sample(s) in the routine EM program

END