Annex 1 update – Potential changes and impacts on microbial QC automation

PREPARED FOR THE Growth Direct EU users group

Rapidmicro biosystems

November 29, 2021

Agenda

- Introductions
- Annex 1 update
- Significant Micro updates
- Compliance and Automation

Attendees

EU Users Group

Presenters
Valsource

Marc Glogovsky
Senior Microbiology Consultant

Rapid Micro Biosystems

David Jones
Director of Industry Affairs

Annex 1 “The Elephant in the room”.

First Issued in 1989.

Revision proposed in 2012

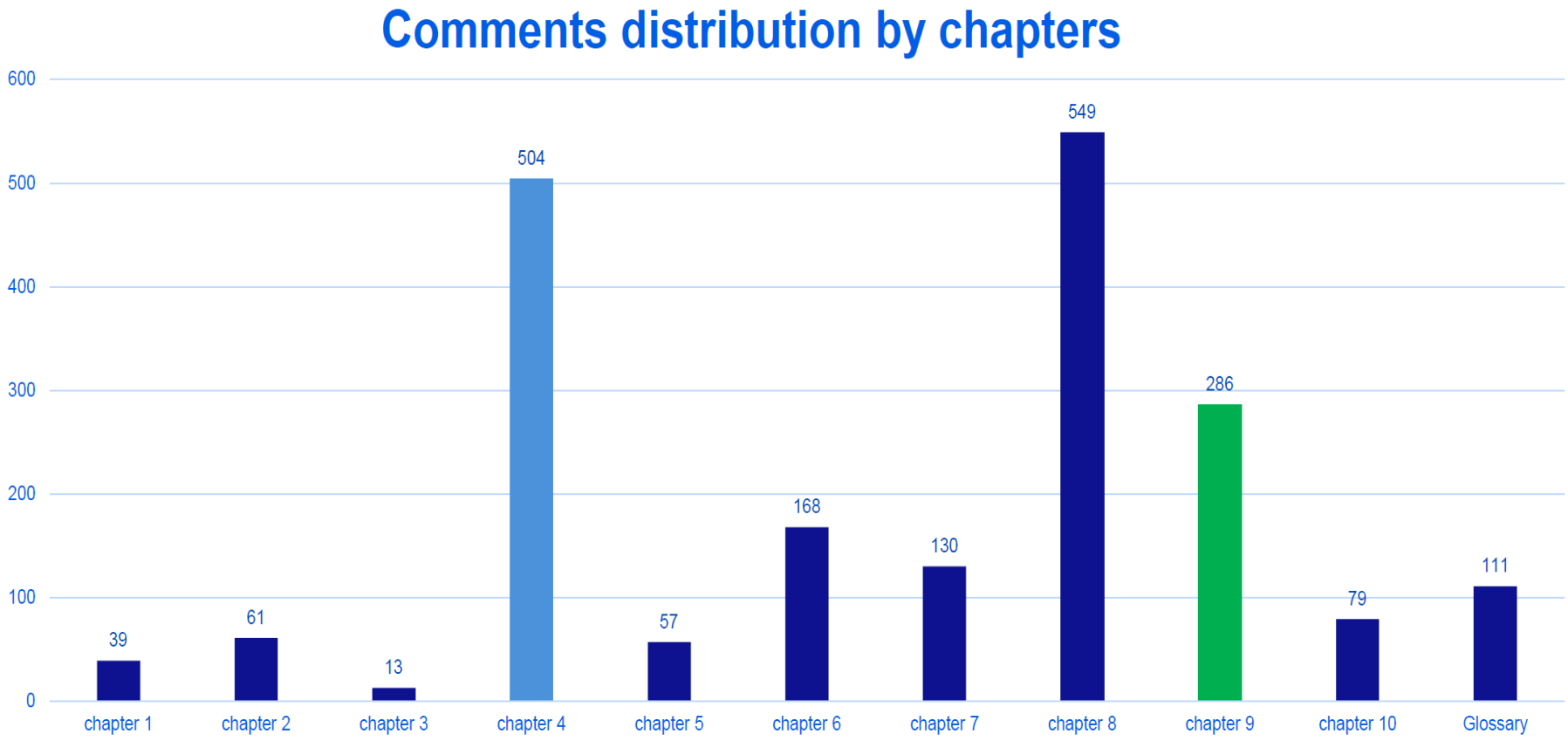
Started in 2014 with a goal to release in 2018 But…..

Public Review in 2017

Re write selected sections
Public Review in 2020

SOON???

Most Controversial Chapters by Comment Count.



Chapters Topics

Ch 8 Production & specific Technologies

- PUPSIT

Ch 4 Premises Isolators & RABS

- Definition “Open”, “Closed”.

Ch 9 Viable & non-viable EM and process monitoring

- Level vs limit,
- Particle size 0.5 vs 5.0µ,
- process simulations.
- CFU defined as standard unit

Annex 1 Microbial Updates®

Marc Glogovsky

EM Site Selection & Frequency

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- Risk assessments should be performed in order to establish a comprehensive environmental monitoring program, i.e., sampling locations, frequency of monitoring, monitoring method used and incubation conditions (e.g., time, temperature(s), aerobic and/or anaerobic conditions).

- **These risk assessments should be reviewed regularly in order to confirm the effectiveness of the site's environmental monitoring program**

Sample Location	Unique Sample ID	Potential Sources of Contamination	Likelihood	Severity	Risk Rank	Comments
Example: Gowning Room	*Example: GR1*	*Example:* • *Bench where operators apply boots* • *Gowning materials brought into to the room*	*Example: Frequent*	*Example: Minor*	*Example: High*	*Example: Risk Rank may indicate sampling frequency and if sampling location is rational.*

LIKELIHOOD		
Rating	**Qualitative Criteria**	**Quantitative Criteria**
Frequent	Failure is almost inevitable	>5 alerts and >1 action in last two trended periods. OR Adverse trend identified in the last two trended periods.
Likely	Repeated failures	3-5 alerts and 1 action in last two trended periods.
Occasional	Occasional failures	1 action level excursion in last two trended periods.
Unlikely	Relatively few failures	1-3 alert level excursions in last two trended periods.
Remote	Failure unlikely	No excursions in last two trended periods.

SEVERITY	
Rating	**Criteria**
Catastrophic	Significant impact to product quality. **Impact to ISO 5 space.**
Critical	Potential significant impact to product quality. **Impact to ISO 5/7 space.**
Serious	Moderate impact to product quality. **Impact to ISO 8 space.**
Minor	Minor impact to product quality. **Impact to controlled, not classified (CNC)** space.
Negligible	No impact to product quality nor the environment (i.e. uncontrolled space).

RISK RANK DETERMINED BY LIKELIHOOD AND SEVERITY MATRIX

Likelihood \ Severity	Negligible	Minor	Serious	Critical	Catastrophic
Frequent	Very Low	High	High	Very High	Very High
Likely	Very Low	Medium	High	High	Very High
Occasional	Very Low	Low	Medium	High	Very High
Unlikely	Very Low	Low	Low	Medium	High
Remote	Very Low	Very Low	Very Low	Low	Medium

Classification vs. Monitoring

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- Potential loss for particle sizes > 1 µm withing sampling system
- Statistical limitation of low particle counts
- Corresponds to removal of 5.0 µm in ISO 14644-1:2015
- Current guideline is “Not Defined”, with no need to establish maximum limits. 2020 draft states that the definitions are not available, however, maximum limits should be set based on a risk assessment and historical data (v13: changes to “not predetermined)

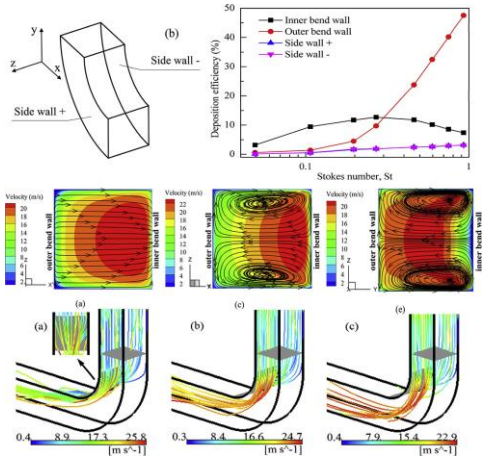

Table 1: Maximum permitted airborne particulate concentration during classification

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	Not applicable	Not applicable
B	3 520	352 000	Not applicable	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[a]	29 000	Not defined[a]

Table 6: Limits for airborne particulate concentration for the monitoring of non-viable contamination.

Grade	Maximum limits for particulates ≥ 0.5 µm/m³		Maximum limits for particulates ≥ 5 µm/m³	
	at rest	in operation	at rest	in operation
A	3 520	3 520	29	29
B	3 520	352 000	29	2 900
C	352 000	3 520 000	2 900	29 000
D	3 520 000	Not defined[a]	29 000	Not defined[a]

Trends & Trend Analysis

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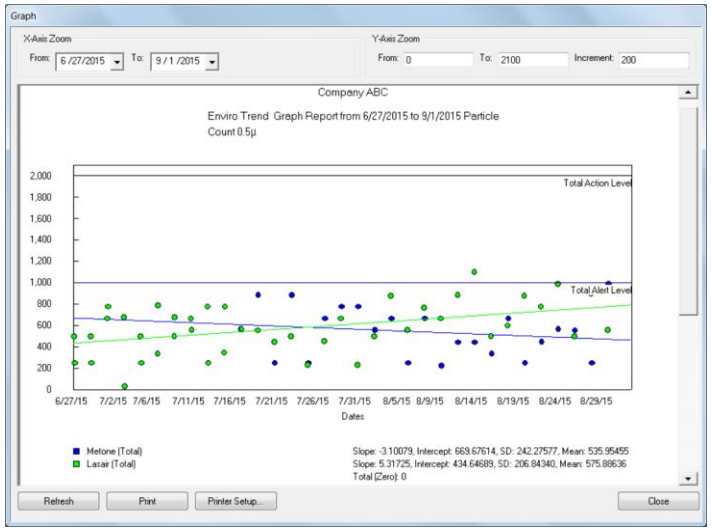
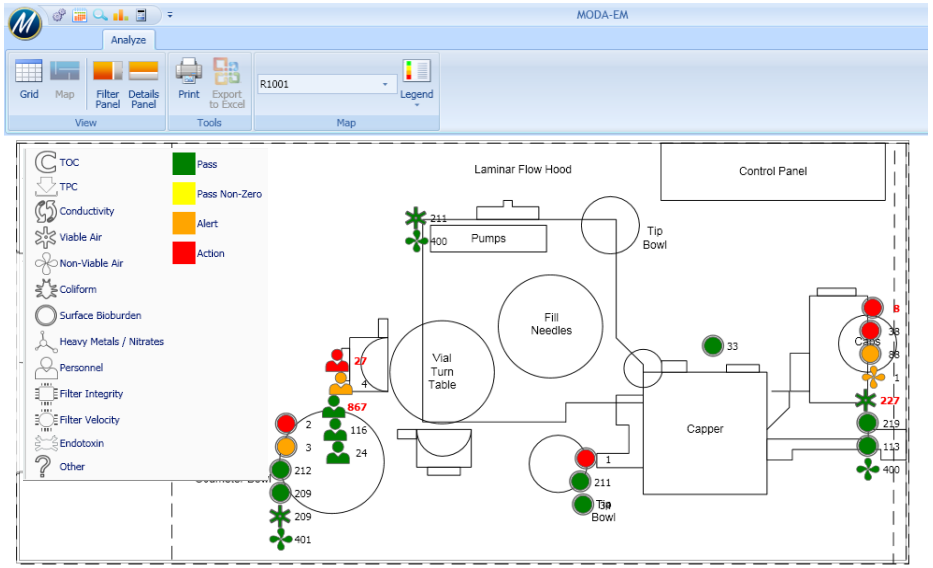
- Monitoring procedures should define the approach to trending. Trends can include, but are not limited to:
  - i. Increasing numbers of action limit or alert level breaches.
  - ii. Consecutive breaches of alert levels.
  - iii. Regular but isolated breaches of action limits that may have a common cause, for example single excursions that always follow planned preventative maintenance.
  - iv. Changes in microbial flora type and numbers and predominance of specific organisms. Particular attention should be given to objectionable organisms or those that can be difficult to control such as spore-forming microorganisms.





Monitoring Equipment

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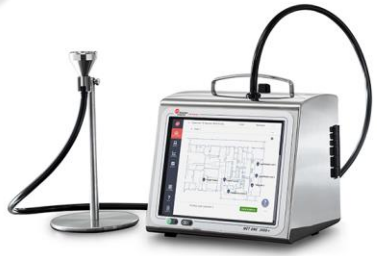
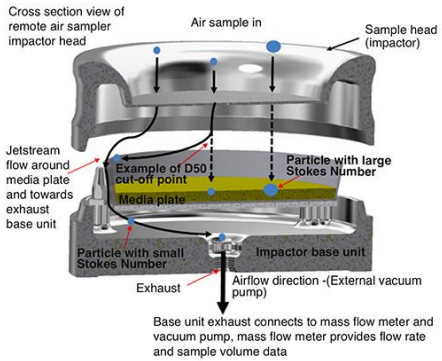
- The Grade A zone should be monitored continuously (for particulates ≥ 0.5 and ≥5 µm) and with a suitable sample flow rate (at least 28 liters (1 ft^3) per minute) so that all interventions, transient events and any system deterioration is captured.

- Sampling methods and equipment used should be fully understood and procedures should be in place for the correct operation and interpretation of results obtained. The recovery efficiency (ISO 14698/BS EN 17141) of the sampling methods chosen should be qualified.



- The size of monitoring samples taken using automated systems will usually be a function of the sampling rate of the system used. It is not necessary for the sample volume to be the same as that used for formal classification of cleanrooms and clean air equipment. Monitoring sample volumes should be justified.



- The method of sampling used should be justified within the CCS and should be demonstrated not to have a detrimental impact on Grade A and B airflow patterns.

Static, Dynamic & Continuous Monitoring

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- Viable particle monitoring should also be performed within the cleanrooms when normal manufacturing operations are not occurring (e.g., post disinfection, prior to start of manufacturing, on completion of the batch and after a shutdown period), and in associated rooms that have not been used, in order to detect potential incidents of contamination which may affect the controls within the cleanroom.
  - **Current version**: Recommended limits for microbiological monitoring of clean areas during operation
  - **Draft versi**on: Maximum action limits for viable particle contamination (does not differentiate)

- Continuous viable air monitoring in the Grade A zone (e.g., air sampling or settle plates) should be undertaken for the full duration of critical processing, including equipment (aseptic set-up) assembly and filling operations. A similar approach should be considered for Grade B cleanrooms based on the risk of impact on the aseptic processing.

Operator Monitoring

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- (V13: 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 (v13: 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 (v13: gloves and gown) .

- (V13: 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.)

- Contact plate limits apply to equipment room and gown surfaces within the Grade A zone and Grade B area.

Operator Monitoring (continued)

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"There are billions of germs, bacteria, and microbes living on my body...but I still get lonely sometimes."

- Personnel gloves (and any part of the gown that may potentially have direct impact on the product sterility (e.g., the sleeves if these enter a critical zone) should be monitored for viable contamination after critical operations and on exit from the cleanroom

- Microbial monitoring of personnel in the Grade A zone and Grade B area should be performed to assess their aseptic behavior. Where filling operations are manual in nature e.g., hand filling, the process in its entirety may be considered as one critical intervention. In these cases, the frequency of microbial monitoring of gowning should be based on scientific principles and justified as part of the CCS. (v13: Where operations are manual in nature (e.g., aseptic compounding or filling), the increased risk should lead to enhanced emphasis placed on microbial monitoring of gowns and justified within the CCS.)

Utilization of RMMs

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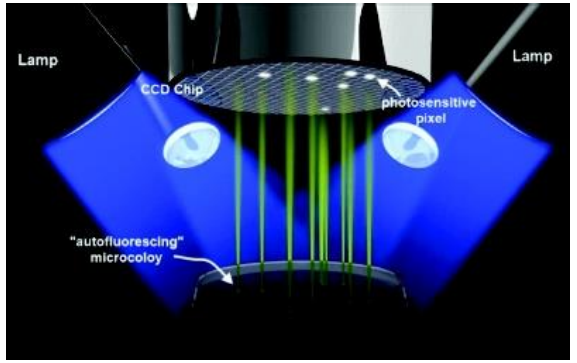
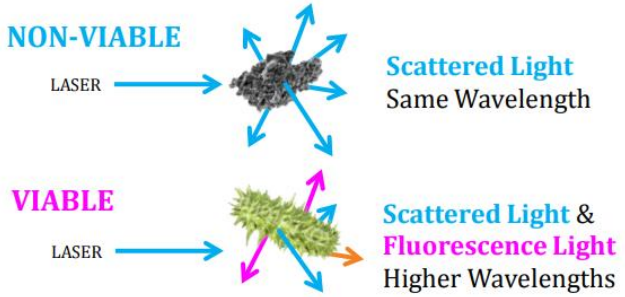
- Limits are applied using CFU throughout the document. If different or new technologies are used that present results in a manner different from CFU, the manufacturer should scientifically justify the limits applied and where possible correlate them to CFU.

- The adoption of suitable rapid or automated monitoring systems 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 methodology.





Compliance and Automation

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Most Common EM Inspection Findings

- Very important to understand the limitations of EM testing
- Absence of recoveries from viable monitoring does not mean absence of contamination
- Often see weak or deficient EM rationales
- Locations not based on process understanding
- Total particle monitoring
  - Not appropriately positioned
  - Tubing too long or tight radius/folded.
- Results not reported in a timely manner
- Lack of reaction to results
- “only 1cfu recovery”….

Alan Moon MHRA, PharMIG 2021

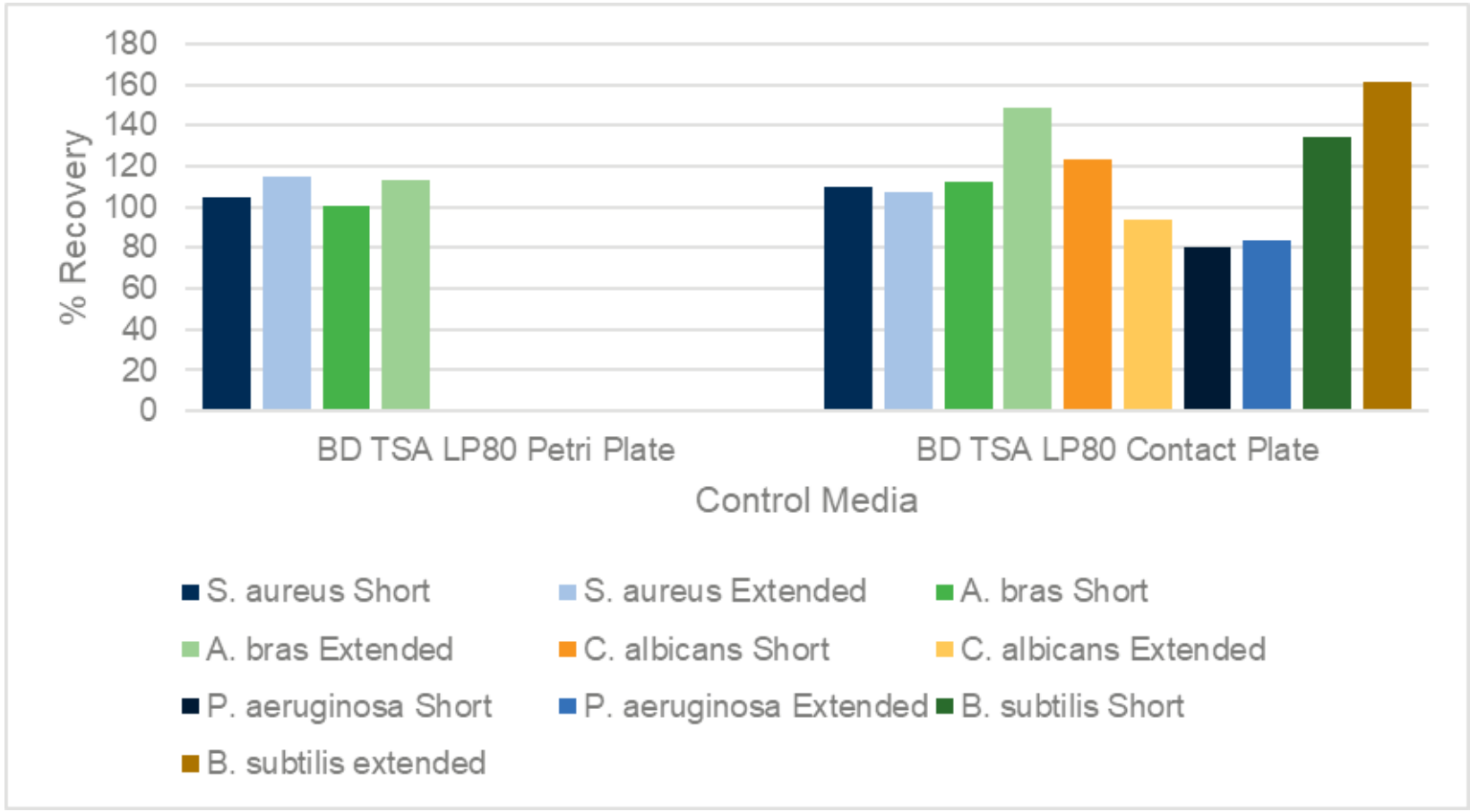
“Remove the Human” “Find organisms faster”

2.i Facility, equipment and process design should be optimized, qualified and validated according to the relevant sections of the Good Manufacturing Practices (GMP) guide. The use of appropriate technologies (e.g. Restricted Access Barriers Systems (RABS), isolators, robotic systems, rapid microbial testing and monitoring systems) should be considered to increase the protection of the product from potential extraneous sources of particulate and microbial contamination such as personnel, materials and the surrounding environment, and assist in the rapid detection of potential contaminants in the environment and product

4.3 Restricted Access Barrier Systems (RABS) and isolators are beneficial in assuring the required conditions and minimizing the microbial contamination associated with direct human interventions in the critical zone. Their use should be considered in the CCS. Any alternative approaches to the use of RABS or isolators should be justified.

“Continuous” Active Air sampling

Organism Recovery



MAS and SAS Samplers

Extended active air sample:

Compares 10 min to take 1m^3 vs 4 hr to take 1m^3 collection time.
Organisms spiked post sampling.

Gelatin filters an option?

Continuous Real Time Microbial sampling

Continuous viable air samplers:

- Azbil, TSI, PMS and *New*- Plair Rapid-C

Continuous Water testing

- Azbil and Mettler Toledo

AZBIL (previously known as BioVigilant), 10 years trying to get acceptance!

Presentations at PDA, Pharmig, Pharmalab all in 2021

HAS THEIR TIME FINALLY ARRIVED?

Automation effect on EM test volume

Closed Robotic Fill Isolators

Questions & Answers

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