DIGITALIZATION AND AUTOMATION OF THE ENVIRONMENTAL MONITORING PROCESS IN C&GT MANUFACTURING GMP FACILITIES: SOLUTION TO LEVERAGE QC OPERATIONAL EFFICIENCY, COMPLIANCE AND OPTIMIZE RESOURCES ALLOCATIONS

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ABSTRACT

Microbial Environmental Monitoring (EM) is crucial to assure patient safety. The visual end point reading of petri dishes has been used for decades without a true performance assessment. Besides, there is growing interest in EM automation technologies.

In today's pharmaceutical industry, there is myriad and high volume of GMP data being generated in the field of EM. This is a challenge, considering the increasing demands to perform further additional testing. The latest regulations are emphazing the requirement for improved data integrity to ensure that facilities are maintained in a state of GMP compliance. Data integrity is not restricted to electronic records and electronic signatures (as described in CFR 21 Part 11); it should be considered as a holistic and consistent approach, taking into account the role of people, processes, and technologies. We will explore data integrity principles and discuss how automation and digitalization of the EM process allows a facility to i). better oversee the quality control process, ii). decrease the numbers and length of investigations, iii). eliminate low value, manual, error-prone tasks and iv). increase the confidence of regulatory agencies in the facility's quality systems.

EM CHALLENGES CAN LEAD TO LABOR-INTENSIVE PROCESSES WITH EXPENSIVE CONSEQUENCES

HEAVY PROCESS & STAFF MANAGEMENT

30% of an operator workload is dedicated to manual documentation of EM controls.[1]

ECONOMIC PRESSURE

Between 2 - 5 product batches are scrapped each year due to Out Of Specification {OOS) EM events.[1]

ECONOMIC PRESSURE

EM annual investigations costs can rise up to 400.000€ with more than 10% linked to data integrity issues.[1]

GAP OF COMPLIANCE

Typically, 132 days are dedicated to audit preparation.[1]

MATERIAL, METHODS, RESULTS AND BENEFITS FOR AUTOMATION & DIGITALIZATION

EM AUTOMATION AND DIGITALIZATION CAN HELP REDUCE DATA INTEGRITY ISSUES

A Six-sigma green belt consultant from bioMérieux evaluated the current EM workflow from 5 Top pharmaceutical companies by following EM QC daily operations in their operations (planning > sampling > incubation > reading) and mapping each step of the EM workflow. The consultant identified and confirmed with the operators the sources of data integrity gaps (framed in red below).

The same approach has been followed using **3P® ENTERPRISE.** This ecosystem includes the EM culture media (**3P® SMART PLATES**), an EM software (**3P® CONNECT** EM module), and the **3P® STATION** (Figure 2), an innovative system developed and validated in collaboration with microbiologists from major pharmaceutical companies. From sampling to trending, take control of your EM process with an end-to-end, fully digitalized and automated workflow.

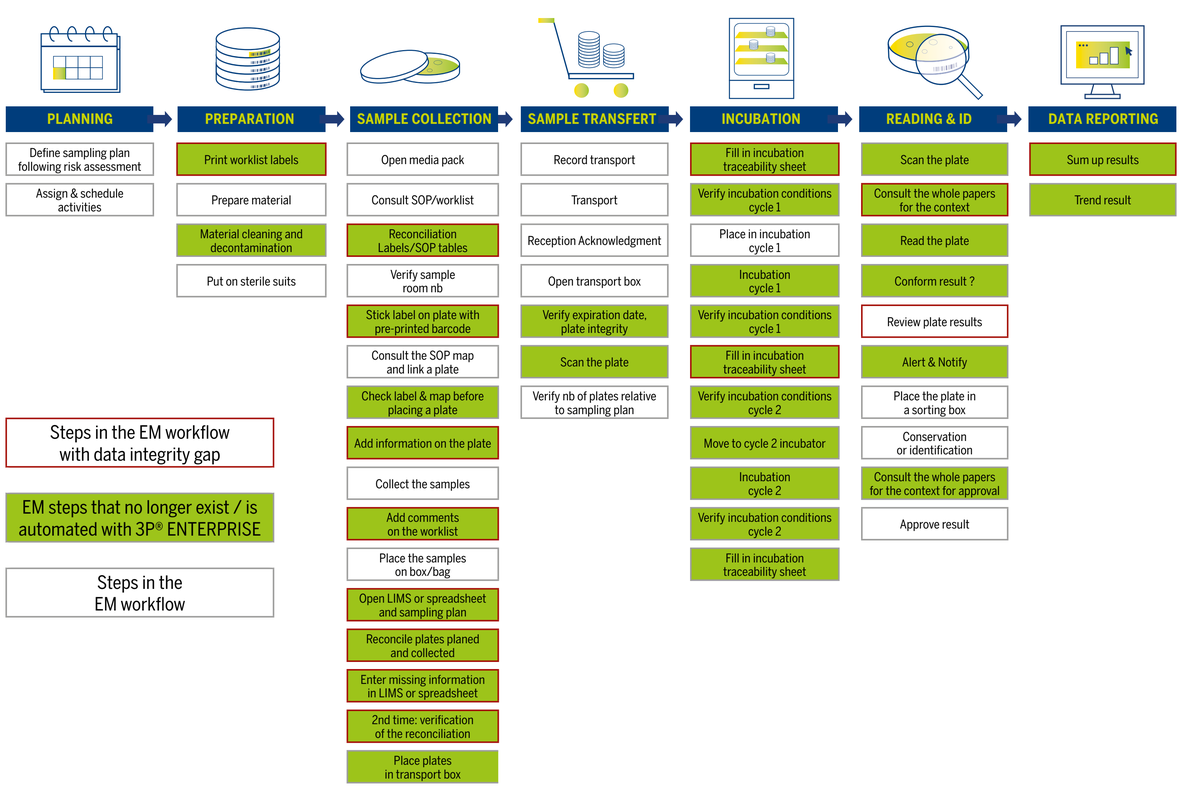


Figure 1: Assessment of the EM workflow before and after automation and digitalization

MAIN OUTCOMES OF THE ANALYSIS

Reduction of data integrity (DI) gaps has been reported and shared with each customer for discussion. From those assessments, **3P® ENTERPRISE reduces the number of DI investigations by 88% [77% - 100%],** which could end up in **35.000€ of cost saving by year[1].**

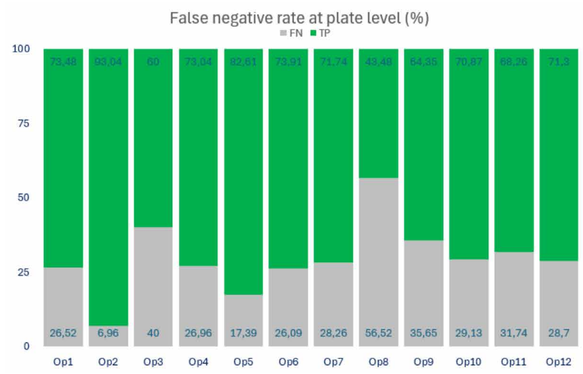
DI gaps have significant impacts and could result in costly FDA warning letters (average cost of 220.000€)[2] and unnecessary investigations.

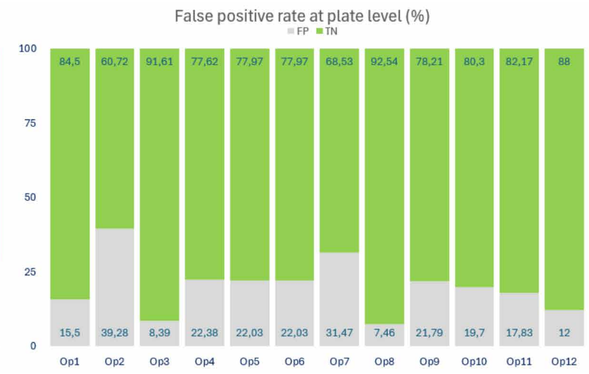
[1] bioMérieux internal analysis based on market survey (n=40 customers; 66% traditional pharma products, 17% Cell & Gene therapy,17% Bioproducts)
[2] A Bad 483 Could Cost a Company Millions | Redica Systems;
[3] bioMérieux 3P® ENTERPRISE microbiological performance summary report
[4] bioMérieux internal "In vitro EM study"
[5] GMP Annex 1: *§ 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. »*
§ 10.10 « Manufacturers of [short shelf life] products should consider the use of rapid/alternative methods. »

EM AUTOMATION AND DIGITALIZATION CAN HELP REDUCE COUNTING VARIABILITY ISSUES

The 3P® STATION is an automated Petri dish incubator/counter, which will reduce counting variability.

We observed significant variability between operators for false positives (FP) and false negative (FN) results just at the plate level:





This system can incubate plates in a range of temperature between 20 and 35°C with a precision of +/- 1°C. and can follow the growth of the microorganisms that are present on the surface of the dishes all along incubation. Equivalency of Counting performances were thoroughly validated (Table 1).

Performance attribute	Metric		Target	Test details
Accuracy *(vs reference count)*	Linear regression	R^2	> 0,95	Absolute comparison
		Slope	[0,9 ; 1,1]	Absolute comparison
		Intercept	[-1 ; 1]	Absolute comparison
	Linear regression		[90%-110%]	Absolute comparison
Limit of detection *(vs traditional method)*	False negative rate @ colony level		Equivalent to traditional method	Z-test @ 95% confidence level
	False negative rate @ plate level		0	Absolute comparison
Specificity *(vs reference count)*	Recovery rate per strains		> 90%	Absolute comparison
	False positive rate @ plate level		Upper bound of CI < 10%	95% confidence level

Table 1: Performances attributes: metrics and associated acceptance criteria [3]

With **3P® ENTERPRISE, dramatically decrease the number of errors due to To Numerous To Count (TNTC),** overgrowth, merging colonies (e.g. Figure 4) and atypic colonies (e.g. Figure 3).

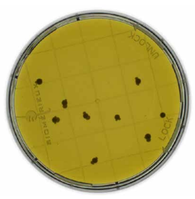


Figure 3: Corynebacterium tuberculostearicum

Figure 4: Bacilus colonies morphology

Figure 2: bioMérieux 3P® STATION

EM AUTOMATION AND DIGITALIZATION CAN HELP REDUCE COUNTING VARIABILITY ISSUES

Real-time data capture and traceability to ensure 21 CFR Part 11 compliance

Timelapse of colony growth on the plate to demonstrate the right count even with merged or overgrown colonies

User guidance at every step

Trending and reporting tools

Counting variability reduction

All data and images are centralized and available anytime

100% of critical data integrity gaps corrected and secured (Figure 1)

CONCLUSION

Updated regulation and guidelines recommends the use of automation to improve robustness and efficiency of petri dish reading.[5]

The automation of the incubation and reading of Petri dishes is an opportunity **to accelerates Time To Result (TTR) and Time To Detect (TTD) thanks to kinetic reading.**

By centralizing data, digitalization coupled with automation solution could also reduce the time and cost dedicated to[1]:

Activities	Average cost per year[1]
Conduct EM investigations	400.000€
Prepare internal and external audits	8.000€
Read EM Plates and documents EM controls	200.000€ (100k plates)
Peaks of activities	93.000€

By automating and digitalizing the EM process using 3P® ENTERPRISE, number of DI related investigations were reduced by 88%, which enable **QC operations to meet higher standard of compliance.** 3P® ENTERPRISE also **leverages QC operational efficiency** and **optimizes resources allocation.**