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MASTER THESIS

The Impact of Digitalization on Environmental Monitoring: Streamlining Processes and Impact on KPIs in Pharma

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Abstract

Pharmaceutical companies operate within strict frameworks for the non-negotiable product safety and purity. Ensuring product purity is the collective output of personnel, machinery and environment operating at optimum conditions where consistent testing and timely alerts enable precision of monitoring. This thesis explores the importance of high throughput automated digital transformation in the Environmental Monitoring (EM) within the pharmaceutical companies. A vital, and currently, manual, time-consuming and cumbersome testing process employed for ensuring product purity. Shifting from manual methods and low throughput data analysis protocols towards digitalized systems -software and automated readers-, demands investment of both capital and time and thus understanding its impact is essential. The manual model of testing is described and compared to the digitalized, using the bioMerieux 3P Connect Software solution as a reference for discussing the benefits of automation. The different key performance indicators (KPIs) that drive decision-making towards automation, such as workflow optimization and data security, have been collected from literature and discussions with key stakeholders. Consulted pharmaceutical companies were derived from different steps of digital transformation, and identified regulatory compliance, operational efficiency, and cost optimization as key components of a sound digitalization system. Data derived from these companies were used to illustrate the urge for transition to digitalization. As with every step towards change, the most common concerns were raised and discussed here along with digitalization strategies designed to satisfy them, underscoring the benefits of EM automation.

Keywords

- Environmental Monitoring (EM)
- Quality Control (QC)
- Key Performance Indicator (KPI)
- European Pharmacopeia (EP)
- Contamination Control Strategy (CCS)
- Good Manufacturing Practices (GMP)

Scope Of Thesis

The points involved in the manual EM testing workflow highlight the challenges of the current gold-standard system where manual data entry can be cumbersome, time-consuming, and prone to human error. The thesis reviews methodologies of environmental monitoring, focusing on KPIs of digitalization as a means of transitioning from manual processes towards the real-time, efficient, error proof, regulatory compliant, fourth industrial revolution (Industry 4.0). Industry 4.0 follows mechanized (Industry 1.0), electricity supported (Industry 2.0), automated through computational power (Industry 3.0) production modes and is founded by two major components, that of connectivity and big data processing. The main aim of the thesis is immerse into the impact of digitalization on EM in the pharmaceutical industry, focusing on how automating these processes can streamline operations and improve KPIs including workflow efficiency, reduction of out-of-specification (OOS) incidences, and data integrity. Data of the digital transformation process of 5 pharmaceutical companies have been used in the description and discussion of KPI performances. These ranged on digitalization stage: from those that have already implemented digital EM solutions, to those in the process of implementing, and those that have yet to explore digitalization in this area. In this context identified important KPIs include *EM Workflow Optimization (1)*, *Out-of-Specification Incidences (2)*, *Data Integrity and Security (3), Regulatory Compliance (4), Improved Resource Allocation (5)* and *Overall Cost Efficiency (6).* Additionally, concerns related with transition to digitalization are examined in the context of how they are being effectively targeted and mitigated in this novel digitalization ecosystem.

1. Introduction

1.1 Industry 4.0 and Pharmaceutical Quality Control Guidelines

Microbial environmental monitoring (EM) is a key component in the pharmaceutical quality assurance (QA) process within the broader context of quality control (QC) strategies. Both QA and QC work synergistically to secure safe and effective pharmaceutical product release to the market; the first (process-focused) by defining, documenting and setting the quality foundations, and the latter (product-focused) by testing the final products against those quality criteria set [V, Balaram. 2017].EM refers to the systematic process of measuring microbial and particle contamination in production and cleanroom areas ensuring product quality and safety along the industrial manufacturing processes [GMP Insiders, 2024]. There is a fundamental distinction between environmental control and environmental monitoring that must be made. The first focuses on maintaining specific conditions within cleanrooms and the latter emphasizes on evaluating the cleanliness by gathering of data [GMP Insiders, 2024]. Ultimately, this data collection process enables an understanding of the microbiological control levels identifying and pinpointing areas in need of preventive and/or corrective actions. Contamination in controlled production areas poses risks not only to product quality but also to patient safety and thus a robust EM program is an essential element of the pharmaceutical industry's operations to safeguard final drug product sterility, potency, and quality otherwise financial status and organizational reputation are at stake (as described in Figure 1). To put this scenario into a real instance, Genzyme's 2010 microbial contamination crisis of its bioreactors led to production halts and drug shortages along with the cost of a 175-million-dollar penalty and a consent decree [Pollack, 2021]. This incident illustrates the high stakes of inadequate contamination control, underscoring the critical role of robust EM programs in mitigating such risks.

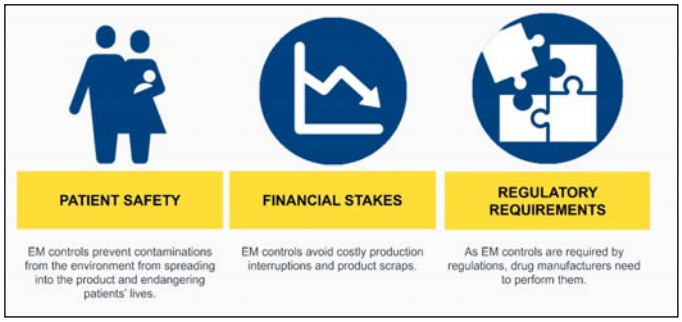

Figure 1: Key Drivers for Environmental Monitoring (EM) in Pharmaceutical Manufacturing: Patient Safety, Financial Stakes, and Regulatory Requirements.

EM employs various methods to detect microbial contamination, including traditional culture-based approaches and modern rapid techniques. To address contamination risks effectively, the guidelines prioritize the detection of microorganisms outlined in the pharmacopoeia, including *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis*, and *Candida albicans* - as significant strains due to their potential for growth in cleanrooms, their resilience, and their relevance to pharmaceutical product safety and compliance [Haleem, R.M. et al. ,2015]. Traditional EM methods are usually carried out through culture growth microbiological tests using sterile, irradiated media such as Trypticase Soy agar (TSA) and Sabouraud Dextrose agar (SDA), designed to cultivate bacteria and fungi, respectively and accounting for 80-85% of total testing in QC controlling processes of pharmaceutical industries [Haleem, R.M. et al. ,2015]. The types of monitoring include air, surface, personnel and water, each serving a specific purpose for identifying potential sources of contamination in the production environment. Growth and culture-based techniques provide a baseline for assessing the presence of viable microorganisms. However, these approaches face limitations as the selectivity of culture media can restrict detection to targeted organisms, overlooking potential contaminants, and the reliance on visible growth means that certain critical microbes may escape identification. On the other hand, rapid record-rich and trace-efficient methods, such as quantitative real-time polymerase chain reaction (qPCR), ATP bioluminescence and metagenomics, offer advanced capabilities, including the identification of non-culturable but viable microorganisms. BioMerieux, within the broader context of its extensive activities in the field, has recently developed and validated technologies that deliver rapid results with increased sensitivity.

After COVID-19, the digital evolution has highlighted the necessity to advance the different

aspects of industrial operations, from manufacturing practices to supply chain logistics, via incorporating smart and compatible digital tools in order to remain competitive, enhance revenue forecasting and support long-term growth. The old, product-oriented business model which relied primarily on revenue streams from patented drugs with market exclusivity, is being challenged by rising biosimilars competition and escalating patient demands for more affordable solutions Arnold, J., 2023]. Patent-monopoly strategies do not support long-term business continuity as new AI-powered approaches to drug development pave the way to tech-enabled healthcare delivery faster and at lower cost. The growing demand for supply of new, complex drug development, asks from professionals in the pharmaceutical industry to optimize operations with the greatest challenge being the un-clinging from outdated manual processes to control compliance risks but also mainly to compete and innovate in the rapidly evolving industry. Shifting into a value-driven and technology-enabled business model, requires integration of automated digital tools and data-driven decision-making to strategically support the long-term sustainability and business continuity [Parida V., et al 2019]. Failing to transition into this new model means losing relevance within the industry, risking being sidelined by competition that offers data-driven and patient-centric drug delivery. As the pharma industry faces growing challenges, digitization holds tremendous potential in helping companies adapt [Hole, G. et al, 2021].

Pharma 4.0 is a “wave” describing the integration of advanced digital technologies in the pharmaceutical industry to enhance manufacturing, simplified compliance and decision-making. In this digitalized framework, Pharma 4.0 leverages IoT (Internet of Things), AI (Artificial intelligence), machine learning and real-time data-analytics enable flexible and efficient production processes for delivering safe, high-quality drugs in a shorter timeframe [Parida V., et al 2019]. In the transformative wave of Pharma 4.0, data is continuously gathered throughout all stages of the manufacturing process, relying on predictive models and automated QC for proactive issue detection [Lee, J., et al, 2019]. As a result, improvement of quality assessment along with facilitation of automated production operations allow for comprehensive QC and risk management. The importance of Contamination Control Strategy (CCS) for sterile medicinal product manufacturing is reinforced via this digital maturity which promotes integrating Quality Risk Management (QRM) principles for a risk-based approach [Kallan D., 2024]. Pharma 4.0 recognizes and addresses the specific regulatory compliance requirements of the pharmaceutical industry. For instance, the principle of “data integrity by design” ensures that

data is accurately collected and securely stored in compliance with regulatory principles of GMP and ALCOA+ standards [Kelly, J., 2024]. This interconnectedness of technology, processes and personnel, promoted by Pharma 4.0, targets compliance and monitoring but most importantly lays the foundation for operational agility and efficiency of the pharmaceutical manufacturing landscape.

1.2 Guidelines of good practices for EM practices

The implementation of an EM program is governed by regulatory frameworks, like the European Pharmacopoeia (EP) and the updated Annex 1 of the Good Manufacturing Practices (GMP). These guidelines make EM a mandatory process in the production and quality control of medicinal products recommending its establishment and integration into a broader CCS -a comprehensive approach that aims to systematically minimize the risk of contamination in cleanroom environments and throughout the manufacturing process [European Commission, 2022] -the industry sets and follows. Typically, these programs involve monitoring of non-viable particles, viable particles (environmental and personnel) and aseptic process simulation (for aseptically manufactured products only), climate monitoring (temperature, humidity) to secure product stability and prevent conditions that encourage microbial growth validating the effectiveness of contamination control measures) [GMP Insiders, 2024].

As digital advancements reshaping the industry, automation of EM has emerged as a top priority for maintaining compliance of cleanroom environments and controlled areas within strict regulatory standards. Thorough risk assessments empower organizations to proactively identify and address potential risks, maintaining desired sterilization levels, validating sampling location selection, minimizing contamination risks, enhancing product quality and safety.. As pharmaceutical companies strive to improve efficiency and reduce prospect production mishaps, EM digitalization offers significant potential for streamlining processes, enhancing performance, and ensuring data integrity. These EM programs and their advancements prepare the pharmaceutical industry to face regulatory audits by agencies such as the European Medicines Agency (EMA) or FDA, which demand accurate, complete, and timely EM data, critical to compliance [Haleem, R.M. *et al.* 2015]. The strong focus on audit preparedness serves as a justification for continuing reliance on traditional manual methods-which still prevail- and the industry's cautious adoption of digital EM tools. However, manual testing methods have been accused of being time-consuming, prone to errors, and

challenging when it comes to ensuring full compliance and traceability.

The 9.4 section of Annex 1 suggests that an EM program should be established and documented to support routine batch certification, as well as periodic assessment during process reviews and investigations [Kallan D., 2024]. The document further emphasizes the importance of comprehensive CCS integrating risk assessments, real-time monitoring, and data-driven decision-making. To achieve this, performance risk assessments are crucial to define EM components like, i.e. sampling locations, frequency of monitoring, monitoring methods, and incubation conditions [Jonathan, B., 2023]. They should leverage insights into facilities, equipment, processes, identifying main high-risk areas in Grade A and B environment [Jonathan, B., 2023]. These risk assessments are regularly subject to review with the aim to confirm the effectiveness of the site's EM program and ensure alignment with the CCS objectives [Jonathan, B., 2023]. Routine monitoring of cleanrooms, clean air equipment and personnel should be performed in operation throughout all critical stages, including equipment set-up [Kallan D., 2024]. The potential benefits of EM automation including increased process control, faster response times to deviations from product quality standards, and more efficient compliance with regulatory standards align closely with the goals set forth in Annex 1. The key aspects of Pharma 4.0 such as digitalization of operations, data integration and analytics, continuous monitoring, and personalized medicine, challenge the traditional paper-based practices of EM heavily.

1.3 Manual EM testing practices

Manual EM testing involves collection of samples and culture-based diagnostics according to standardized protocols, followed by accurate data documentation. The frequency of testing is dependent on the production shifts and the internal Standard Operating Procedures (SOPs) that a pharmaceutical company sets and reviews according to their manufacturing schedule [Albrecht, B. et al., 2023]. The culture media intended for use during this test must pass a conformity check (material sterilization, expiration check, label printing). The QC team creates files that include dates, lot numbers of materials to-be used, designated sampling points and type of sampling method to be employed. This process relies heavily on manual documentation and involves a series of labor-intensive procedures, with paper documents following from t0 this cumbersome process. Sterile irradiated culture media plates are used for passive (air collection monitoring airborne contamination) and active (direct contact

machine operator's hands / gowns/ equipment surface points, active air samplers in critical points) sampling for a specified duration. Once sampling is complete, the culture media is collected, securely transferred for incubation, and later observed, count and doublechecked by a laboratory analyst that proceeds with recording the colony-count on paper and on a digital file such as Excel. If the colony count findings exceed acceptable limits its colonies will potentially be tested for identification to species level if found within grade A or B (acceptable limit <1) according to the EP, documented as part of the broader EM testing record [Albrecht, B. et al., 2023]. When examining the process shown in Figure 2 in detail, it becomes clear that the critical checkpoints are grounded in regulatory requirements, designed to ensure the compliance-driven nature of the process.

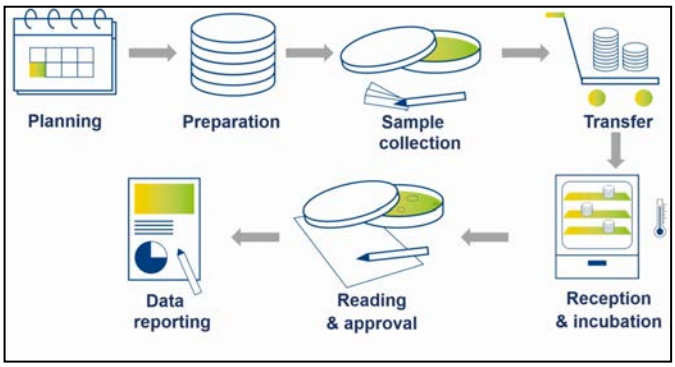

Figure 2: Summary of typical EM testing steps from scheduling to data reconciliation.

The procurement and inventory departments play an essential role in managing the stock of EM required materials (EM media), ensuring their timely acquisition, efficient storage and safety stock levels to support continuity of the testing processes. The stock management serves as a preliminary step, tracking sterile media lot numbers, expiration dates and approved growth-promotion tests ready to be handed to the QC teams for use in EM testing. It is important to monitor lot traceability, by batch and lot number, which is documented and tracked for future reference, particularly in the event of deviations or positive microbial findings. There are different testing schedules dictated by manufacturing activity, where certain areas prone to higher contamination risk are being monitored more frequently. The dedicated QC team is responsible for preparing the EM plan outlining sampling points, types of sampling and time intervals (Figure 3).

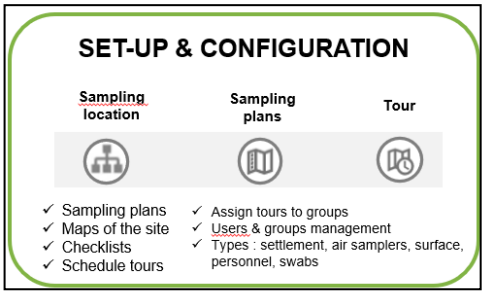

Figure 3: Set up and Configuration steps in the EM workflow.

Settle plates (passive air monitoring) are placed in cleanrooms or production areas for a defined period, typically during production runs. These plates collect airborne particles that settle naturally and allow testing of cleaning agents' efficacy. Contact plates are used for direct surface monitoring, often on operators' hands, gloves, gowns, and high-touch equipment. In addition, active air samplers forcefully draw air over media plates to capture any airborne microorganisms. Once the sampling time has elapsed, the plates are securely collected, documented, and transferred to the microbiology lab for incubation under strictly controlled conditions. A controlled incubation marks an important checkpoint as the collected plates are placed in incubators, where they remain for predefined periods (typically 5 – 6 days), usually under two different temperature conditions (e.g., 20-25°C and 30-35°C), allowing for the recovery of a wide range of bacteria, yeasts and moulds [Poloni et al., 2023]. After incubation, the plates are visually inspected for colony growth where analysts carefully count the colonies, document their number on paper, and enter them into digital records.

Upon completion of incubation, the colonies grown need to be counted and recorded. These records are initially registered on the designated papers that follow the medium in the sampling point, and subsequently entered in a digital system (commonly Excel or basic databases) for data integrity purposes and to minimize human error, a second analyst or a supervisor reviews the data to ensure accuracy. This step is open to data entry challenges as manual transcription errors are common and can lead to inaccurate records. If the colony counts exceed acceptable limits (depending on the cleanroom grade), further investigation is triggered. The results upon QC analysts' review are being approved by the QC supervisor marking the end of the sample workflow lifecycle (Figure 4).Samples with positive findings undergo microbial identification. In critical areas such as Grade A or B zones, positive colonies are often subjected to further testing to identify the microorganism down to the species level involving advanced techniques. These results are recorded and compared against historical data to determine if the contamination poses a significant risk. According to 9.14 of Annex 1,

action limit excursions should have a Root Cause follow up and alert excursions should have a process within the SOP to follow [Jonathan, B., 2023].

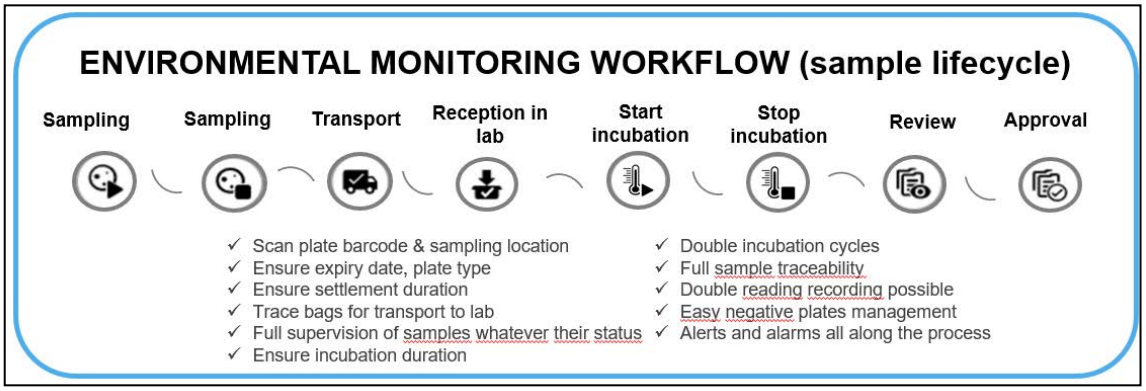

Figure 4: Full Environmental Monitoring workflow from sampling to approval.

Monthly and Quarterly Reports summarize the collected data in regular reports, which are used for internal reviews and regulatory audits. Also, at the end of the year, a comprehensive report is generated to identify trends in contamination levels over time. Trending helps determine if contamination sources are under control or if further corrective actions are needed [Albrecht, B. et al., 2023]. Data comparison, critical areas track record, and effectiveness of cleaning ensure ongoing compliance and monitoring of manufacturing practices. At times of trends show increasing contamination, action plans are created for improvement. The data derived from EM testing (sampling points, results, OOS investigations) is stored and filed for regulatory audits, including both the paper records and digital copies. The risk of lost/incomplete data originating from the nature of manual systems makes the retrieving of accurate information challenging.

Traditional, manual EM practices are likely to be more error-prone facing data traceability and integrity issues, compared to more sophisticated digital EM methods which are designed to minimize them.

Figure 5: Thee 3 main impacts of deviations that can be encountered during the EM process; Investigations, Corrective/Preventive actions and Potential product loss. All these aspects are impactful side-effects of positive findings during EM testing.

1.4 Model of Full Digital Solution for EM and the Example of bioMerieux Offer

According to the increasing demand for digitalization of EM, suppliers (software and instrument vendors) are positioning their solutions to meet current and anticipated market needs. The focus extends beyond initial implementation, emphasizing a seamless transition into automation while fostering partnerships through on-going support., Although there is a big range of options on the market, for the purpose of this thesis, taking a deeper look into bioMérieux's offering will be utilized as an example of a full digital solution for EM enabling the discussion of how can such digital ecosystems integrate into current practices and what are the benefits automation brings. Vendors such as Sherpa, Biotrends and Lonza have

developed softwares to automatize EM testing steps and facilitate reporting and trending. Other vendors have invested in high-quality incubators with integral camera systems to capture the microorganism growth andcreate digital records of finidngs. The ecosystem bioMerieux has developed, encompasses three levels; gamma-ray irradiated culture media, EM software and EM reading station(s), with its architectural design relying on 21 CFR 11 compliance and its intention to facilitate current error-prone, laborous practices as a 360o approach.

Considering the previously discussed manual steps (summarized in Figure 6), the software automatically and instantly collects, tracks, and saves all the actions and data related to EM. This replaces the paperwork process and minimizes the risk of human-errors, saving time during the entire EM process. Ultimately this enables companies to make reliable decisions, maximize efficiency and ensure compliance with regulatory standards.

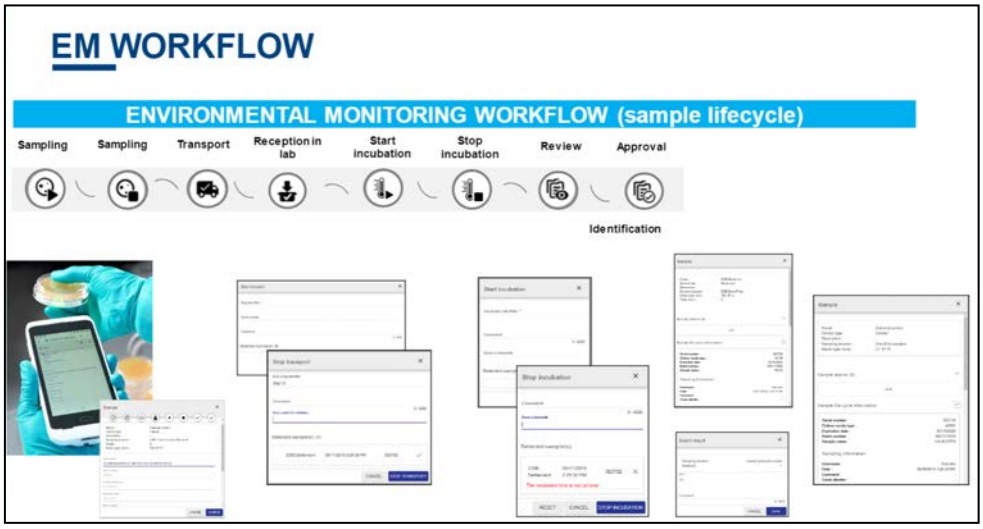

Figure 6: Scanning of plates at sampling locations – tracking across the testing lifecycle

For the final steps of the manual EM, a reading station provides the automation lacking in the tedious task of plate visual inspection post-incubation. 3P® ENTERPRISE is an end-to-end solution for digitalization and automation, that automates the incubation and counting of microbiological colonies on EM Petri dishes in real time (Figure 7). This comprehensive solution includes the 3P® SMART PLATES and the 3P® STATION – an instrument which, connected to 3P® CONNECT Software, allows to automate critical steps and get reliable results with dedicated services to ensure easy and faster the implementation and validation and keep the operation running smoothly.. A combination of high-performance algorithms and high-

definition images taken every hour mean that there is a standardized reading of plates - no human error - and alerts raised should a sample exceed its specification, allowing rapid corrective actions. The solution is able to deliver significant efficiency gains. Not only are all the manual reading steps, currently undertaken in a laboratory, removed, but as the 3P® STATION can be placed much closer to the manufacturing floor, incubation can start sooner and therefore results obtained more quickly, allowing users to take the right action, faster.

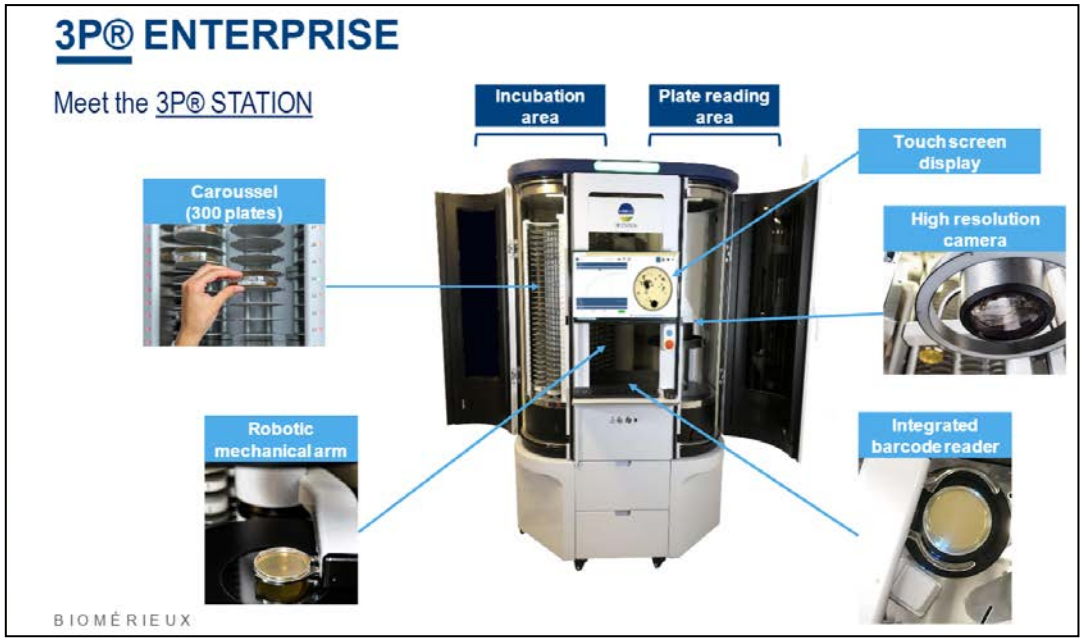

Figure 7: Automated reading in the incubator and data import in the software.

1.5 Scope of the thesis

The points involved in the manual EM testing workflow highlight the challenges of the current gold-standard system where manual data entry can be cumbersome, time-consuming, and prone to human error. The thesis reviews methodologies of environmental monitoring, focusing on KPIs of digitalization as a means of transitioning from manual processes towards the real-time, efficient, error proof, regulatory compliant, fourth industrial revolution (Industry 4.0). Industry 4.0 follows mechanized (Industry 1.0), electricity supported (Industry 2.0), automated through computational power (Industry 3.0) production modes and is founded by two major components, that of connectivity and big data processing. The main aim of the thesis is immerse into the impact of digitalization on EM in the pharmaceutical industry, focusing on how automating these processes can streamline operations and improve KPIs including workflow efficiency, reduction of out-of-specification (OOS) incidences, and data integrity. Data of the digital transformation process of 5 pharmaceutical companies have

been used in the description and discussion of KPI performances . These ranged on digitalization stage: from those that have already implemented digital EM solutions, to those in the process of implementing, and those that have yet to explore digitalization in this area. In this context identified important KPIs include EM Workflow Optimization (1), Out-of-Specification Incidences (2), Data Integrity and Security (3), Regulatory Compliance (4), Improved Resource Allocation (5) and Overall Cost Efficiency (6). Additionally, concerns related with transition to digitalization are examined in the context of how they are being effectively targeted and mitigated in this novel digitalization ecosystem.

2. EM Digitalization and the Pharmaceutical KPIs

2.1 Pharma industry KPIs – drivers for decision making in the pharmaceutical digital transformation.

The traditional EM process is cumbersome due to the sequential nature of tasks; from the preparation of materials, sampling, and incubation, to reading and recording results, each step involves manual intervention, which increases the total time required. Interviews with 5 pharmaceutical companies, ranging from full paper-based practices to fully automated plate monitoring and reading stations, resulted in the top selection of the six most important KPIs. These KPIs have been defined as the drivers for decision making in the pharmaceutical industry with regards to digital transformation. They include **workflow optimization**, **OOS incidences**, **data integrity and security**, improved **resource allocation**, **regulatory compliance**, and **overall cost efficiency**, covering the most critical areas of performance and compliance for digitalizing EM.

SMART Analysis of Key KPIs in EM Digitalization

KPI	Specific	Measurable	Achievable	Relevant	Time-bound
1. EM Workflow Optimization	Streamlining EM process by reducing the manual steps and automating data collection.	Quantification of time savings per step in the process, % reduction in human error, and automated result accuracy.	Adoption of automation tools and seamless integration with existing systems.	Efficiency enhancement, human error reduction, and EM cycle shortening.	Tangible improvements within 6-12 months post-implementation.
2. Out of Specification (OOS) Incidences	Minimizing OOS occurrence through automation and real-time alerts.	Tracking OOS frequency, investigation duration, and corrective actions before vs. after digitalization.	Predictive monitoring and automated alerts for preventing deviations.	Reduction in production downtime and compliance-related risks.	Targeting a 30-50% reduction in OOS cases within 12 months.
3. Data Integrity and Security	All EM data is traceable, tamper-proof, and available for audit.	Monitor compliance with ALCOA+ principles and regulatory audit success rates.	Implement digital records, automated logs, and control-based access.	Essential for regulatory compliance and upholding GMP standards.	Ensure 100% digital compliance within 6 months of system integration.
4. Regulatory Compliance	EM digitalization alignment with Annex 1, GMP, and data integrity guidelines.	Measure regulatory audit readiness, % of deviations due to compliance issues, and corrective action efficiency.	Use pre-validated EM software and automated documentation.	Ensures continuous compliance and minimizes regulatory risks.	Target full compliance with Annex 1 updates within 12 months.
5. Improved Resource Allocation	Shifting human resources from repetitive EM tasks to higher-value QA activities.	Measure reduction in labor hours spent on EM, % of staff reallocated, and efficiency improvements.	Automate EM sampling, tracking, and reporting to permit focus of skilled personnel.	Maximizes productivity and lowering operational costs.	Optimize resource use within 6-9 months of system implementation.
6. Overall Cost Efficiency	Cost reduction associated with OOS investigations, labor, and production downtime.	Assess financial impact through annual savings quantification from less deviations, faster investigations, and reduced labor cost.	Implement EM automation with defined ROI metrics.	Strengthens financial sustainability and validate necessity for digital investments.	Positive ROI achievement within 2-3 years post-implementation.

Out of the 5 companies interviewed 1 (Company X) allowed, through laboratory consultancy, to retrieve actual data linked to their routine testing practices. Along with the production and QC teams, a bioMerieux expert followed all daily practices with the goal to calculate workflow optimization and translate it into time lost over registering data. In a closer look to the case study of Company X, the workflow optimization was quantified in terms of time spent on different tasks and extrapolated on one full year. These data are described in each KPI as a quantification example of the indicator's impact.

2.1.1 EM Workflow Optimization

The workflow optimization KPI directly addresses the need for efficiency in a process-heavy industry. By streamlining workflows through automation, companies not only improve productivity, but also reduce the risk of human error, aligning with both regulatory compliance and operational goals. There is increased emphasis in the reviewed Annex 1 chapters for implementing changes to achieve a streamlined, risk-based approach in the EM. Inefficiencies or manual labor related bottlenecks can lead to delays, increasing the risk of contamination or non-compliance, posing operational efficiency as a key target for improvement within the context of a high-stake environment of the pharmaceutical production. The key elements in achieving this target are sample tracking automation, manual interventions reduction, and cycle time optimum enhancement. A software-driven sample management permits real-time monitoring and traceability without the risk of delays for lost media or samples throughout the process as seen in Figure 9. Also, the fewer touchpoints by the personnel performing the sampling, transfer, and handling of media, the less the risk of contamination and faster throughput, aligning with Annex 1's guideline emphasis on CCS. The cycle from sampling to corrective action is highly shortened when automated reading is implemented on the final reporting step. This KPI is translated into improved overall response time providing flexibility in data handling through faster processing and digital reporting.

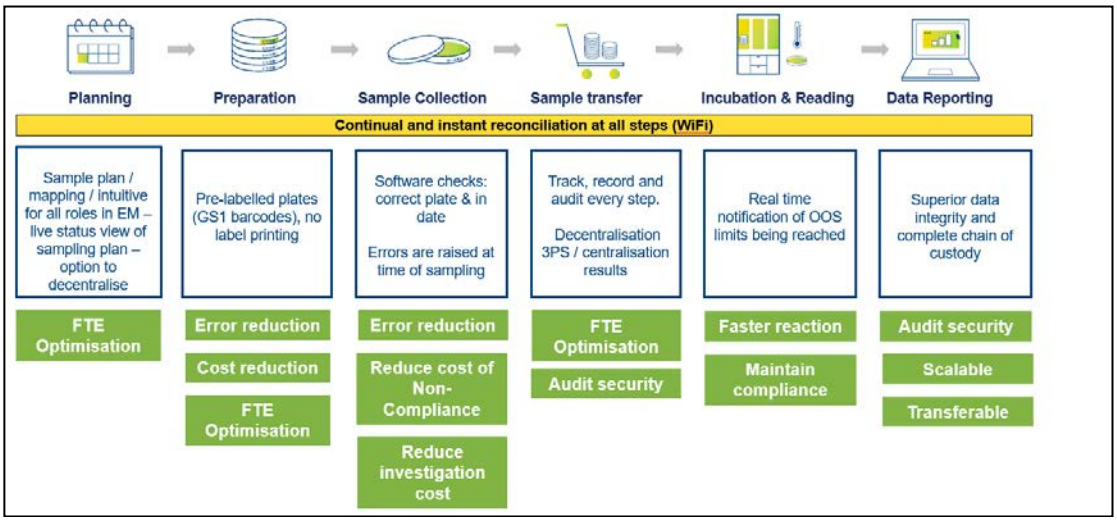

Figure 9: The different benefits of automating the steps involved in EM testing from planning to data reporting. The advantages listed characterize a continual and instant reconciliation at all steps.

During the lab consultation at Company X, time to complete tasks was reviewed where the incubation cycle for samples takes up to 6 days (144 hours), with a double incubation at different temperature ranges (72 hours at 20-25°C, followed by 48 hours at 30-35°C). Additionally, manual counting and reconciliation of plates add significant time delays, especially since deviations are often detected only after incubation. X's implementation of the automated incubator-reader, 3P STATIONs, would allow for faster processing by streamlining incubation and analysis near the production site. The reduction in manual steps—from 29 to 14—drastically cuts down the time spent on each phase of the EM process and illustrates that automation in both sampling and data handling speeds up reporting via reducing the total cycle time.

Initially, the workflow involved 29 steps, including manual labeling, plate handling, and data entry, which introduces the potential for human error. Plates were only reconciled after incubation, adding to inefficiencies. Upon implementation of digitalization, the number of steps was reduced by 52% (from 29 to 14) through automation. For instance, MODA (bioMerieux vendor competition) manages sample tracking digitally, reducing manual intervention steps during incubation. Additionally, placing 3P STATIONs close to production avoids unnecessary transport of plates, eliminating several non-value-adding steps, which results in significant time savings and reduced error risks.

2.1.2 Out-of-Specification Incidents (OOS)

The OOS incidences are directly correlated to the final product quality and the contamination control—both crucial for compliance with Annex 1 guidelines [Arnold, J. (2023]. Such incidences where EM results, like microbial counts, exceed predefined limits and signaling potential contamination or operational issues, translate into costly investigations where production halts and, at times, there is product recall. Therefore, keeping OOS incidences to a minimum maintains operational continuity and ensures product quality/patient safety.

In manual or semi-automated processes, deviations often go undetected until the end of the incubation period or during data review, which delays corrective action. However, with automated monitoring systems, deviations are detected in real-time. As soon as the environmental parameters (e.g., microbial counts, temperature, airflow) exceed acceptable limits, the system triggers alerts allowing teams to respond immediately and contain potential contamination before it escalates.

Furthermore, both data collection and analysis are substantial markers of OOS incidences. The risk of human error in manual data entry, such as transcription mistakes and missed or delayed entries, is responsible for missing OOS events or worse, leads to incorrect investigation paths [Stumpff, J.P., 2020]. On the other hand, working on an automated system in a unified platform, provides a continuous live monitoring of critical parameters aiming to ensure that data is accurate and entered contemporaneously. This enables quicker identification and response as real-time traceability guides informed investigations.

Besides the beneficial approach to collecting and visualizing data, software automation offers the subtle advantage of predictive analytics, a key valuable aspect of digital transformation. Moving ahead of traditional EM practices that lead to reaction to OOS events upon occurrence, predictive analysis through automated systems permits detection of patterns and trends in EM data that may signal an impending OOS incident. By identifying potential issues before they cross specification limits, companies can implement proactive measures, such as adjusting environmental conditions or recalibrating equipment, as a means of prevention from OOS events. Given that investigation processes following an OOS incident are often lengthy and inconsistent, depending on the manual interpretation of data from different sources (e.g., lab records, spreadsheets), the subsequent decision-making and corrective action to follow are delayed. On the contrary, an automated EM system streamlines the root cause analysis by providing a single platform that aggregates all relevant data. Predefined workflows guide teams through the investigation process, ensuring a more systematic and efficient approach to identifying the root cause of the OOS event.

To date, pharmaceutical companies that have not yet transitioned into an automated EM system, quantify this KPI of OOS incidence rate through the total number of occurrence, the response time into the OOS event, the time spent on root-cause analysis (investigation) as well as the efficiency of the corrective actions implemented (such as cleaning, adjusting environmental conditions, or recalibrating equipment) until normal conditions of production are fully restored [Stumpff, J.P., 2020]. The digitalization of EM testing permits streamlining of investigations where real-time monitoring can potentially reduce investigation time by 30-50%. For instance, if an OOS investigation typically takes 5 days (40 working hours), digitalization could cut this down to 2-3 days (16-24 working hours) leading to the total saving equal to up to 24 hours per incident. Subsequently, when OOS incidents are flagged in real-

time, corrective actions which frequently include cleaning, adjusting environmental conditions, or recalibrating equipment, can be implemented immediately, potentially preventing a full production shutdown [Haleem, R.M. *et al.* 2015]. If a corrective action typically takes 2-3 days to resolve, real-time alerts and automation can reduce this to less than 1 day.

Aiming to further enhance the benefits of saving time with quick information flow and reaction time, one could look at the cost savings these translate into. Investigating an OOS incident typically requires the collective time and effort of several departments, including QA, QC, Production, and often external consultants or auditors. Based on an average industry labor cost of X euros per hour for these employees, a typical manual investigation might take 40 hours, involving 2-3 employees, costing around X x 40 euros per OOS event. The reality where automation is implemented could make investigation time be reduced by 30-50%, significantly lowering the cost per event. In the unfortunate scenario of production halting and product wasted, this extrapolation is very impactful with lost revenue. Depending on the scale of the facility, downtime costs can range from 10,000€ to 100,000€ per day, considering factors such as product batches total scrapping, labor costs, and equipment downtime. Considering that a 3-day production halt due to an OOS incident might cost a facility 30,000€ to 300,000€ where minimizing the production downtime to 1 day reduces the cost to 10,000€ to 100,000€. In sterile pharmaceutical production, and even more in the bioproduction, the cost of losing a batch can be substantial, and hence automation brings the value of preventing entire batch loss along with reducing waste.

Finally, the ultimate cost-demanding case involves repeated OOS incidents triggering regulatory action and product recall. Inspections, warnings and even fines pose the risk of brand being publicly exposed and economically charged with fines that range from 100,000€ to several million euros, depending on the severity of the violation. When the OOS incidents necessitate product recalls, which are both expensive and damaging to the company's reputation. The average cost of a recall in the pharmaceutical industry is around 10 million euros, but it can vary widely based on the product, market size, and impact.

2.1.3 Data Integrity and Security

The strict regulatory environment under which the pharmaceutical industry operates,

emphasizes this KPI of data integrity and security as a central key point in maintaining compliance. Data integrity refers to the accuracy, completeness, and consistency of data throughout its life cycle [Cooke, E., 2021]. Data security ensures that the information related to pharmaceutical processes—especially sensitive production and environmental monitoring data—is protected from unauthorized access, tampering, or breaches [Kumar S., et al, 2020].

Traditional EM practices, which often involve manual data collection, sample testing, incubation, and result interpretation, are not only time-consuming but also prone to human error. These processes typically generate massive volumes of data, much of which must be meticulously registered, stored, and maintained for regulatory audits. The sheer complexity of handling this data through paper-based systems or basic digital spreadsheets increases the risk of data integrity issues—from transcription errors to misplaced or incomplete records. Ensuring the accuracy and security of data through digital systems protects against regulatory fines and product recalls. For example, if a contamination is found in a Grade A cleanroom, the company must trace the exact location, time, and personnel involved, as well as the specific conditions that led to the contamination. Any failure to provide real-time, accurate data could lead to regulatory action such as the ability to automatically track and document every change made in EM data, ensuring full transparency.

Digital transformation seeks to support the pharmaceutical companies satisfy the expectations of regulatory bodies, like the FDA and EMA, to follow the ALCOA+ principles (Figure 10) in managing data and minimizing the risk of data integrity violations [European Commission, 2022].

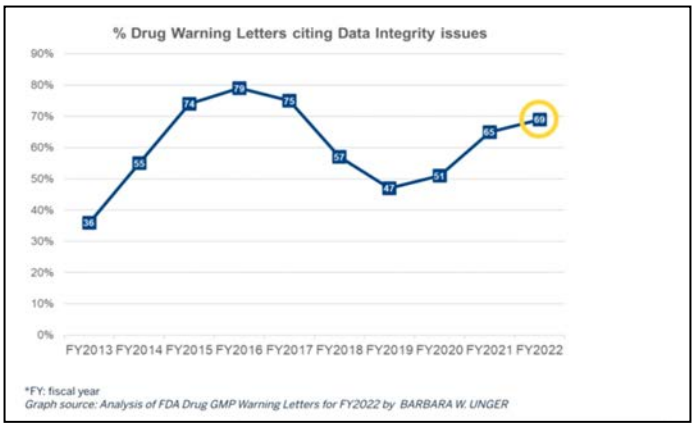

Figure 10: In 2022 about 70% of FDA warning letters cited data integrity issues.

Automated systems ensure that data is entered contemporaneously, directly from

instruments, and is protected from manipulation. Access control protocols (such as requiring user-specific authentication) ensure that only authorized personnel can edit or modify data, and all changes are logged and traceable according to 21 CFR 11 [European Commission, 2022]. Automated systems take into consideration access control metrics which permit the regulated tracking of who has access to what data, and how secure these processes are with features such as multi-factor authentication and restricted user rights. This not only improves data accuracy but also ensures accountability in cases of discrepancies as, although rare, it is very crucial to minimize the number of incidents related to data security issues. Additionally, with digital systems, records are stored electronically, meaning they cannot be lost, misplaced, or altered without detection. Audit trails capture every version of a document, making it easier to demonstrate data integrity during an audit or internal review. Automated data backup at a set frequency ensures that data is regularly and securely backed up to prevent loss or tampering.

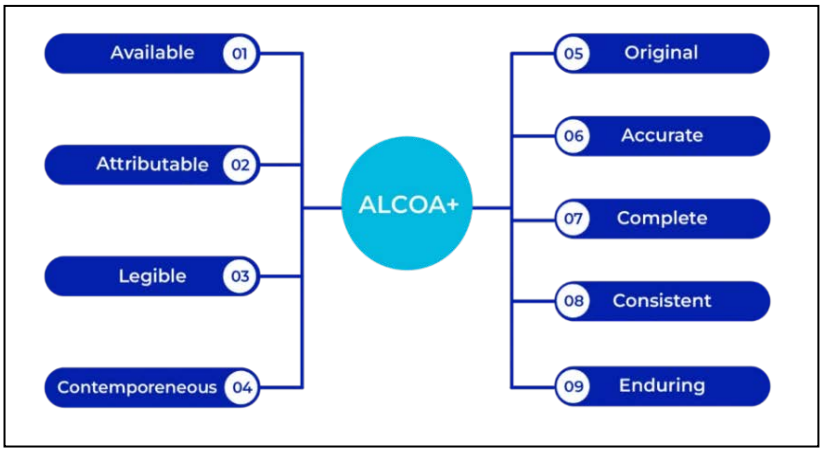

Figure 10: ALCOA+ within the context of pharmaceutical practices describes the guiding set of principles introduced by the FDA in 2010 to ensure data integrity of electronic systems.

In the pharmaceutical industry, data integrity and security are far more than just regulatory checkboxes—they are strategic imperatives that protect patient safety, ensure product quality, and safeguard a company's financial stability [Arnold, J., 2023]. Data integrity failures can result in product contamination, regulatory penalties, legal consequences, and massive financial losses. The most frequent issues reported are usually disabled or non-reviewed audit trails, shredding of records without justification along with inadequate controls over computer systems and hence failure to investigate OOS results. Moreover, maintaining secure and accurate data protects intellectual property, maintains trust with regulators, and supports compliance with increasingly stringent global regulations like Annex 1. Therefore, investing in

automated, secure, and traceable data systems isn't just about avoiding fines—it's about ensuring long-term sustainability and resilience in a highly regulated, high-stakes industry.

Additional benefits were highlighted in the laboratory consultation results of Company X. The utilization rate is yet another parameter that is encapsulated in this KPI. Automation ensures higher uptime and better utilization of incubators and plate readers. By streamlining plate handling and processing within 3P STATIONs, downtime between stages is minimized, and real-time data flow allows continuous monitoring. Predictive maintenance based on digital tracking would further optimize equipment efficiency, ensuring minimal disruption to production cycles. With regards to data integrity, Digitalization eliminated the 12 identified data integrity gaps, reducing them to zero, which is crucial for audit readiness and compliance. Another important variant when qualifying digitalization of a method is the reduction in error steps. In Company X's case, the steps with potential error risks were reduced from 7 to just 1, reflecting a significant decrease in deviations and subsequent investigations. This reduction in manual steps and errors directly correlates with full-time equivalent (FTE) savings, as fewer resources are needed to manage deviations, investigate issues, and handle repetitive tasks allowing better allocation of resources on more important tasks.

2.1.4 Improved Resource Allocation

EM is a labor-intensive process for both production and QC teams because of repetitive and tedious tasks. In a highly regulated industry, resource optimization is not just about saving costs—it's about allocating skilled workers to tasks that add the most value, such as managing contamination risks rather than performing repetitive manual tasks. Resource allocation is more than just a matter of efficiency; it's about maximizing the value of human capital while maintaining strict regulatory standards. Given the complexity and high-stakes nature of pharmaceutical manufacturing, every task must be performed with precision and accountability. However, many EM tasks are repetitive and time-consuming, consuming valuable human resources that could be better deployed elsewhere. Skilled professionals in the pharmaceutical industry should focus on tasks that directly contribute to contamination control, risk management, and critical decision-making [Jonathan, B., 2023]. However, manual tasks, such as data entry, plate handling, and result recording, often take up a significant portion of their time, pulling them away from these high-value activities. Discussions with the managers of QC departments have revealed the acknowledgement and weight of this KPI

summarized in three goals; reduction in personnel time spent on EM tasks, drastic reductions in human errors and cost savings in labor.

Time spent on EM manual steps diverts the team members involved from more critical activities such as risk assessments, contamination investigations, or continuous improvement initiatives. Post-Digitalization, automation drastically reduces the manual handling of tasks such as automated samplers and incubators reduce the need for continuous monitoring and digital data entry systems eliminate the time required for transcription and logging results.

Inevitably, manual processes are prone to human error, especially in repetitive tasks like data transcription, manual readings, or tracking samples. Errors in data entry or recording can lead to significant issues such as OOS incidences, deviations, or regulatory non-compliance, all of which require substantial time and resources to resolve. Automated systems ensure that data is collected, entered, and analyzed with minimal human intervention, significantly reducing the risk of transcription errors or data mismanagement. Automation also ensures data accuracy and traceability, which is critical for audit readiness. The overall impact in the reduction in errors translates to fewer deviations, less time spent on investigations, and fewer corrective actions required, allowing teams to work more efficiently.

The time spent on these tasks not only increases labor costs but also results in opportunity costs, as skilled workers are not fully utilized in areas where their expertise could bring greater value. In the example of Company X, the improvement in productivity, that permits to manage higher workloads with the same workforce, was highlighted by monitoring their process cycle time. Manual counting and delayed reconciliation due to plate transport added inefficiencies and deviations could only be detected after incubation, which elongates the total cycle time. The digitalization impact was reduction of manual interventions and usage of real-time data tracking via digital tools. Re-allocated focus on strategic work, has been estimated to a 15-30% reduction in labor costs, particularly in large facilities where thousands of samples are processed daily. This could lead Company X to achieve an expected considerable gain in time, especially in post-incubation reporting. The automation of sampling, incubation, and result interpretation will lead to quicker cycle completion and faster deviation identification.

Digital tools for EM free up personnel from low-value, repetitive tasks and empower them to focus on activities that enhance contamination control, improve compliance management,

and drive operational excellence. By integrating digital tools that automate routine tasks, companies can unlock significant time and cost savings while ensuring that their most valuable resources, their people, are used to their full potential.

2.1.5 Regulatory Compliance

This KPI ensures that companies meet stringent guidelines like those in Annex 1, reducing the risk of regulatory breaches, shutdowns, or fines. It's a top priority in highly regulated industries like pharmaceuticals. The audit success rate is a very crucial success factor for the pharmaceutical companies highly subject to being facilitated when digital tools enable traceability and data integrity. By improving traceability, audit readiness, and data integrity, digitalization allows companies to maintain compliance more effectively, reducing the risk of regulatory scrutiny and ensuring the smooth operation of pharmaceutical production. Additionally, faster response times to compliance-related deviations and changes in regulatory standards make digital systems essential for maintaining long-term compliance [Cooke, E., 2021]. By ensuring a robust digital infrastructure for compliance, pharmaceutical companies can not only avoid penalties and shutdowns but also maintain market access and enhance their reputation for quality and safety. Pharmaceutical companies demonstrate their accountability to regulators, partners, and consumers when they are capable of safely supporting operational continuity. Some common examples of non-conformity to regulatory requirements include cases where computerized systems have not configured to meet data security and control along with failures to document laboratory records simultaneously and/or deliberately, falsifying manual records.

The selection of the digitalization provider highly depends on trusting that the solution aligns with evolving regulations and ensuring the tool’s proper validation. That is the reason a system (software and reader) with a ready-to-use comprehensive guide on installation (IQ), operational (OQ) and performance (PQ) qualification guidelines by the supplier is a must-have feature. This documentation is set-up by the supplier’s R&D team and provides clear instructions that once completed at the customer’s site, they certify both successful integration as well as annual qualification of the system. In addition, audit-ready features such as “Audit Trail” and “21 CFR 11”, secure data storage and traceability at times of audits [Kelly, J., 2024].

2.1.6 Overall Cost Efficiency

From labor savings to reduced downtime due to fewer OOS investigations, cost efficiency is a pivotal factor of the return of investment (ROI) for the digital transformation of EM testing. As discussed, deviations yield investigations, with the cost of a single OOS event costing up to tens of thousands of euros in terms of labor and lost production time. Reducing the number of OOS incidents can save substantial amounts of money annually. When OOS incidents do occur, digital systems enable quicker identification of root causes and faster corrective actions [Chopra, V. 2011]. This limits the downtime associated with deviations and allows production to resume faster. This KPI is essential for management buy-in and long-term sustainability. Digital transformation involves upfront costs, including the purchase of automated EM systems, data management software, and training for staff. These costs can be substantial, depending on the scale and scope of the implementation. Over time, the ongoing savings from improved efficiency, fewer errors, reduced labor, and minimized product waste make up for the initial investment.

ROI= Annual Financial Benefits − Initial Investment / Initial Investment ×100

According to quanitifications originating from data discussed with Company X, the following example approximations are provided here. The total annual savings are ~400.000€ (OOS Savings: 150,000€, Labor Savings: 100,000€, Downtime Savings (lost production days): 150,000€), in order to quantify this ROI the calculation incorporates the pricing model, which includes initial investments (implementation, validation, and training) and annual recurring costs (license and support), illustrating the financial viability of digital EM solutions.

2.2 Additional KPIs for consideration as drivers for selection of digital transformation vendor partner

In addition to the core KPIs defined, there are a few more points raised by the pharmaceutical industry representatives providing a holistic view of the **digital transformation** process in EM, taking into consideration market demands, transition needs, and adaptability.

2.2.1 Target Market Alignment

Different pharmaceutical companies have varying needs depending on their size, location, and

regulatory jurisdictions. A digital solution's relevance depends on how well it fits the target market (large multinationals vs. small local producers) which is significantly differentiated both by operational scales and resource capacities. The vast amount of data generated across multiple facilities requires a highly integrated and harmonized solution to reconcile and analyze data efficiently. These companies may also require greater customization in their digital EM systems to seamlessly integrate with existing machines, filling equipment, and Laboratory Information Management Systems (LIMS). Adoption readiness plays a key role in decision-making towards EM digitalization adoption, particularly for the companies less advanced in their digital transformation journey. As discussed during the interviews, these organizations prioritize the ease of implementation and the integration with existing systems when evaluating new solutions. Such solutions fit the market best as they facilitate quicker adoption while thriving for consistent performance across different customer segments, supporting their long-term success. It is important that the solution enhances user satisfaction by addressing specific operational needs and simplifying compliance- which is an essential factor in such a highly regulated industry as the pharmaceutical. Moreover, offering customizable and scalable features, allows the digital solution to expand alongside the company's growth or evolving regulatory demands, making it a valuable long-term investment.

2.2.2 Setup Demands and Transition Time

A smooth transition from a manual or semi-automated system to a fully automated one is essential for successful adoption. Reduction in implementation time can allow the companies to realize the benefits of the solution quicker, seeing improvements in compliance, data accuracy and overall productivity resulting into a faster ROI. It's not uncommon that prolonged or complex transitions generate not only operational disruptions but most importantly resistance from the end-user employees. One way to mitigate this challenge is to opt for phased rollouts, starting with data capture, followed by automated reporting and eventually reach to full integration. Sustaining a gradual approach minimizes disruptions to existing operations and gives room to early-stage adjustments based on feedback from the users who feel involved in the process and subsequently more engaged.

Additionally, scalability of the system, stemming from its architectural design, can allow the software to grow alongside the company's expansion. In the context of EM programs, the

software should be able to scale seamlessly to accommodate increased volumes of testing and additional sampling points without compromising performance. This aspect comes hand-in-hand with the ease of updates and the room for customization based on evolving needs that ensure the EM framework remains relevant over time.

2.2.3 Training Demands and User Adoption

Sequentially, the success of a digital transformation project often hinges on the employees who use the system which in the case of EM, range from QC staff and production personnel to IT teams. The effectiveness of the transition is directly impacted by the training demands that often pose a significant challenge. Complex software and its integration into existing workflows, can overwhelm staff, especially if the training process is time-consuming or inadequate. As precision and adherence to regulatory standards are essential, employees must not only learn how to operate the new tool but also understand its impact on data integrity, reporting accuracy, and compliance with regulations such as GMP and 21 CFR Part 11 [Kelly, J., 2024]. Resistance to adoption is another major hurdle. Employees accustomed to manual or semi-automated systems may feel insecure or anxious about fully automated tools, especially if they are unfamiliar with the technology or perceive it threatening to their job security. This reluctance can manifest in reluctance to engage with the system, lower morale, or even active resistance, which can lead to delays in the implementation process or improper use of the system, compromising both quality and compliance. In regulated environments like pharmaceutical manufacturing, where precision and accountability are non-negotiable, such resistance can disrupt critical testing processes and extend the time needed to become fully operational.

To mitigate these challenges, companies should prioritize user-friendly software and streamline the training process. Hands-on training sessions, comprehensive documentation, and ongoing support play an essential role in reducing the learning curve. Additionally, involving employees early in the process, demonstrating the tangible benefits of the system, and addressing concerns about job security can increase buy-in and reduce resistance. By positioning the software as a tool that enhances their roles rather than replaces them, companies can foster a more positive attitude toward adoption. Furthermore, a robust change management plan, with defined roles and timelines, can ease the organization through the transition. This plan

should include not just technical training but also cultural and organizational support to ensure smooth integration. Over time, as the workforce gains confidence with the system and recognizes its benefits, resistance diminishes, and adoption accelerates, ultimately ensuring effective transition.

2.2.4 Installation and Operational Investment

The installation and operational expenses are significant considerations for pharmaceutical companies as even if digitalization promises calculated long-term savings, the initial upfront investment can be a barrier to adoption. The cost of validating the software and the automated reader is one central parameter taken into consideration in the qualification process of selecting a partner. For pharmaceutical companies, validation is essential to comply with GMP guidelines and involves Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) all together ensuring that the system meets regulatory standards. The initial validation period could range from 1-3 months and requires a re-validation per substantial software update. Besides time-consuming, the validation period is often costly. In some cases, validation expenses can make up 30-50% of the total setup cost due to the need for detailed documentation and repeated testing [Jonathan, B., 2023]. Partnering with vendors who provide validation packages and specialize in GMP-compliant solutions can streamline this process.

With regards to the operational costs, there is an expected downtime which occurs during the implementation. Initial integration of a digital EM system may require partial shutdowns or reduced production capacity for setup, calibration, and training, which can lead to 1-2 weeks of downtime. However, downtime can be minimized by conducting implementation during low-demand periods or scheduled maintenance. Aiming to mitigate long operational disruptions, companies may implement temporary backup systems or keep the manual process operational in parallel until the automated system is stable. Some facilities also establish “shadow systems,” where digital and manual methods run simultaneously for a short period to ensure data consistency and troubleshoot issues. Companies need to balance initial costs with long-term operational savings, and this can be actualized through clear cost-benefit analyses that help with justifying the transition to automation.

2.2.5 Adaptability to Regulatory Updates

How easily can the system be updated to comply with new regulations (e.g., changes in Annex 1 guidelines or new data security laws)? And how quickly can the system adapt to new regulatory demands? Regulatory requirements, particularly in the pharmaceutical industry, are constantly evolving and thus the digital systems must be agile and able to rapidly implement updates to remain compliant. The ICMRA statement emphasizes the critical role of communication and collaboration between the pharmaceutical industry and regulatory bodies in enabling flexible and efficient change management. To comply with evolving standards, regulatory frameworks are needed to facilitate adaptability [Cooke, E., 2021]. By fostering open communication and setting clear protocols, regulators and manufacturers can collaboratively address challenges like data integrity, system validation, and compliance, which are foundational for adapting to new technologies [Cooke, E., 2021].

This KPI is critical to characterize the need for an adaptable system with proactive preparation for regulatory changes rather than reactive response that governs today. This agility is especially vital in high-risk zones (e.g., Grade A and B areas) where strict contamination control is mandatory. Companies can leverage real-time system updates for compliance, reducing the time and resources spent on manual adjustments or temporary workarounds that could compromise data accuracy or process integrity. Moreover, automated audit trails help maintain detailed records, improving transparency and simplifying the overall audit process. This reduces the risk of violations related to data integrity, documentation, or procedural inconsistencies, which are common audit findings in facilities with outdated systems.

The key components of an EM software encompass characteristics such as seamless software updates, configurable compliance settings, future-proof design for scalability and scrutiny on data integrity. A system that is adaptable to future regulatory changes ensures longevity and reduces the risk of non-compliance in the face of evolving standards.

2.2.6 Flexibility of the Digital Tool (EM software)

The flexibility of the software is a critical factor, as the industries need to ensure that they are not restricted to a single vendor or specific systems. The ability of EM software to integrate

seamlessly with existing equipment and hardware, such as identification instruments or other automated readers, is essential for achieving comprehensive traceability and simplifying the reporting process. This eliminates manual data transfer, reduces errors, and ensures that all relevant data flows directly into the monitoring system for comprehensive analysis. The software must be scalable to accommodate future expansions or upgrades, ensuring it remains relevant as the company's needs grow. As companies bring in new equipment, the software should easily integrate with these systems without additional configuration or customization.

Instruments used in microbial identification (e.g., MALDI-TOF MS/M, PCR thermal cycler) should be able to automatically transfer the identification results (data import) of any microbial strains found in Grade A and B areas. This ensures compliance with Annex 1, which mandates detailed identification of microorganisms in critical areas and is valuable information for extended report and data visualization across the EM process.
Additionally, the software should support real-time data feeds from multiple instruments, ensuring that all relevant environmental data (e.g., microbial identification, plate readings) is updated continuously. Real-time data synchronization speeds up decision-making processes and allows for quicker corrective actions.

Another important variable is the flexibility in reporting which is essential in providing "custom-made" points of view of the collected data. The software should allow users to customize reports based on regulatory demands (e.g., batch-specific reports, deviation analysis) and company-specific needs. It should also facilitate easy data export for audits and internal reviews.

3. Pharma Industry Concerns

As the pharmaceutical industry navigates towards the transition to automating EM testing, several concerns emerge in discussions shared with candidate vendors. The following three reservations listed reflect a sum of all the frequently raised points during the interviews with the pharmaceutical companies, that are shared among them and provide a good insight into their expectations. By addressing these concerns suppliers can foster greater trust, meet

market demands and support successful adoption of EM automation.

Concern **(1)**: The Cost of Digitalization and Payback Period.

Concerns of financial nature come as natural considerations when evaluating significant technological purchases that are a company's investment. To address this concern, both parties involved (company and supplier) must collaborate to build a robust business case for the management. Once the case is built, aligning with the main KPI concerning the company (i.e. operational efficiency, production capacity, compliance needs), running a pilot first provides an effective way to review it. Focusing on how the solution meets the specific problem permits problem-solving visualization and reinforces trust to the solution [Jonathan, B., 2023].

Additionally, engaging internal allies (stakeholders) aids in influencing the decision-makers. Commonly, in EM digitalization projects the stakeholders driving the progress should be project owners with project management skills along with Quality managers (QC and QA) sponsoring the project, all along close collaboration with IT leaders. All together the goal is to establish a shared vision and secure buy-in at various organizational levels. The cross-functional collaboration among IT, finance and the supplier is necessary for a comprehensive cost breakdown that includes infrastructure, software, equipment (some capitalized, some expenses), implementation fee and the recurrent cost (annual license). This holistic view highlights the solution's profitability and justifies the investment.
An example of a successful business case in one of the interviewed companies was focused on consideration of customer relationship. The case demonstrated how delays to deliveries were linked to OOS events and subsequent investigations. In that approach, while compliance benefits are difficult to be calculated, tracking metrics such as the reduction in number of CAPAs aided in the quantification of ROI. Ultimately, the role of the business case is to pinpoint the link between the identified problem and the business core strategy ensuring alignment.

Concern (2): Resistance to Change and Complexity of Implementation (up to full-system integration).

A very important aspect to this concern is that pharmaceutical industries are not just investing

in a digital system that has a great range of features. EM automation encompasses significant process changes which are often challenging and so the company and the personnel involved heavily relies on provider's expertise [Jonathan, B., 2023]. The supplier needs to be focused on providing support throughout the integration of the digital tool at every stage to ensure a smooth and timely installation and validation. Suppliers like bioMérieux offer valuable services aiming to streamline the processes and provide guidance at every step of the solution's deployment as a partner. From validation guides to on-site turnkey solutions, the role of partnership is to help expedite the implementation of investment by reducing validation time and expense. When the industry is qualifying a supplier, they can't but calculate the cost (labor and time) it will take for this solution to be fully integrated in routine. All the above-mentioned features are responding to the valid concern which reflects resistance to change. URS guides, Risk Analysis documents, IOPQ instructions along with consultancy in the execution of the validation structure a 360 approach to the digitalization project which needs to be adapted into current practices and harmonize with existing systems.

Furthermore, companies often adopt a phased rollout strategy, beginning with simple functionalities like data capture before expanding to advanced features such as automated reporting or full integration with manufacturing systems. This gradual approach minimizes disruptions, allows for iterative improvements, and builds confidence among users, ultimately reducing resistance and accelerating full adoption.

Concern (3): Security and Data Integrity Concerns.

Regulatory compliance with 21 CFR 11 requirements and its evolving framework remain a cornerstone of pharmaceutical decision-making and hence is a typical concern when investing in advanced digital tools. Stakeholders frequently express concerns about whether a supplier's solution meets the requirements outlined in user requirement specifications (URS) and demonstrates a proactive, compliance-driven architecture.

Pharma 4.0 technologies involve the use of advanced systems and software, and regulators need to ensure that they meet the required standards [Lee, J., et al, 2019]. To meet this concern, suppliers integrate features such as audit trail, real-time system updates and

traceability of data produced along with automatic back-ups to ensure documentation accuracy. These features not only simplify the audit process but also minimize risks associated to procedural inconsistencies or data-related violations. Highlighting the compliance-ready and adaptive design of an EM solution pictures a future-proof investment capable of evolving alongside the regulatory demands pharmaceutical companies are asked to face.

4.Concluding Remarks

Digital transition, as also manifested through Pharma 4.0, represents a remarkable opportunity for the pharmaceutical industry to reinforce compliance with the regulatory requirements, such as GMP and ALCOA data integrity standards, enhancing responsiveness to the evolving market demands in new drug development. The digital transformation path, although shaped by high standards, permits flexibility to the companies for integrating combinations of different technologies, tailored to their specific needs, with the ultimate goal to optimize manufacturing efficiency. Tools such as the software and automated reading stations for EM offer increased control over potential risks of contamination, the deviations they create and the recovery times, shifting into a proactive approach of QA/QC. It has been undeniably confirmed by all the companies whose interviews are reported in this thesis, that the timing requires embracing new eras of technology where it does not only monitor processes but also provides valuable insights about trends, predictions and risk assessments. However, it is essential to strategically invest in new technologies upon a thoughtful review of options, carefully weighing the ease of adoption and the solution's ROI. From there, digitalization promises faster and safer product release on the market, supporting the company's scalability and competitiveness.

Like with every change, this transformative shift raises concerns. Ensuring compliance with high standards and guidelines remains a critical factor that pharma industries must continuously address, especially when adopting new digital tools. Also, with increasing data analytics and AI machinery, the data generated by the pharma industry is subject to privacy and security threats. As these concerns become increasingly important, the next key step the industry must take moving forward is to protect its sensitive data, ensuring both digital systems' seamless interconnectedness as well as cybersecurity. Moreover, hiring, training and retaining skilled professionals that have this advanced skill-set related to technology poses another challenge on the industry, as harmonization and fast adaptability are now needed more than ever. Finally, it is in the mindset shift of the decision-makers to trust their digitalization journey by viewing not only as an upgrade but mainly as a necessity for long-term sustainability.

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