Improving the Cleaning Certification Process in the Manufacturing Area

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Abstract *— By addressing the shortcomings and inefficiencies in the present Cleaning Certification procedure used by biotechnology manufacturing companies, this project seeks to modernize and streamline it. The technique experiences lags and disconnects from vital systems like Manufacturing Execution System (MES) and Laboratory Information Management System (LIMS), impacting product release timing. The Define, Measure, Analyze, Design, Verify (DMADV) methodology is used in this project to thoroughly comprehend the current process, gather and analyze data, and create a digital platform that smoothly combines Manufacturing Execution System (MES) and Laboratory Information Management System (LIMS). The initiative aims to increase operational effectiveness, decrease waste, and maintain regulatory compliance by speeding up sample testing and automating the Certification process. A new age of excellence in biotechnology manufacturing is ultimately intended, which will redefine industry norms.*

Key Terms *— Biotechnology Industry, Cleaning Certification, DMADV Methodology, and Lean Manufacturing.*

PROBLEM STATEMENT

The Cleaning Certification process plays a pivotal role within the biotechnology manufacturing industry, ensuring the proper cleaning and validation of equipment used in production. Nevertheless, this process encounters several challenges that necessitate attention and improvement. Firstly, there are recurrent delays in verifying samples within the Laboratory Information Management System (LIMS), which can often last from a week to several months. These delays can profoundly impact product release dates, potentially impeding market availability and operational timelines. Secondly, the Cleaning Certification process, in its entirety, proves to be time-consuming and labor-intensive, replete with manual steps that contribute to inefficiencies in the workflow. Addressing these challenges is essential for enhancing the overall efficiency and efficacy of the Cleaning Certification process within the biotechnology manufacturing industry.

RESEARCH DESCRIPTION

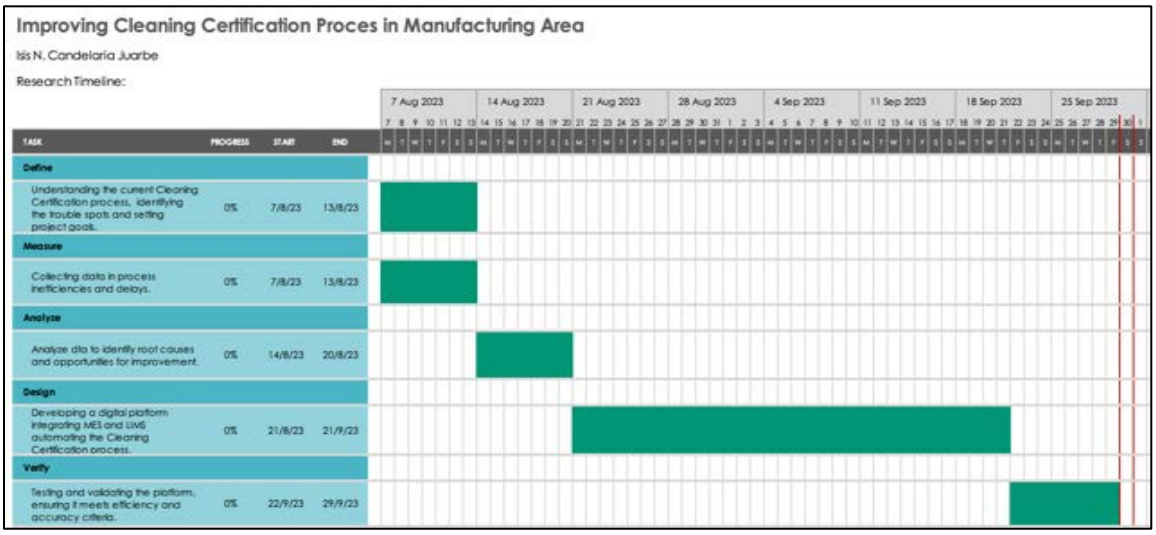
To streamline the Cleaning Certification process in the biotechnology manufacturing industry, this research study applies the DMADV methodology and lean manufacturing concepts. The process is automated and streamlined, eliminating human verifications and cutting down on the time it takes to analyze samples by combining MES and LIMS into a single digital platform. The ultimate objective is to improve Cleaning Certification's operational effectiveness and practicality while integrating lean manufacturing concepts to help the biotechnology manufacturing sector.

RESEARCH TIMELINE

As shown in Table 1, the research project is structured into a logical timeline. In the first phase, Define, which lasts for one week, the focus is on comprehending the intricacies of the Cleaning Certification procedure, identifying problems, and establishing clear project goals. The Define phase will operate concurrently with the Measure phase over the same week while collecting extensive data on workflow delays and process inefficiencies. After data collection, a one-week analysis phase will look at the data to find the sources of problems and indicate potential areas for process improvement. Subsequently, the project advances into the Design phase, which extends over four weeks. During this phase, a digital platform integrating MES and LIMS

Table 1

Gantt Chart Project Timeline



will be meticulously developed to automate and streamline the Cleaning Certification process, reducing the need for manual verifications and enhancing communication with the laboratory. The final phase, Verification, will last one week and focus on the team's feedback about the design concept of the platform. This phase is essential to ensure that the venue meets and exceeds established efficiency and accuracy criteria. This will help to get a Cleaning Certification process that is thoroughly improved and optimized by integrating digital solutions and lean manufacturing principles.

Research Contributions

This research project substantially contributes to biotechnology manufacturing by developing an integrated digital platform designed specifically for the Cleaning Certification process. Integrating MES and LIMS, this platform represents a significant technological advancement that promises to enhance operational efficiency and drive digital transformation in the industry. One essential contribution is the substantial reduction in process delays, resulting in expedited product release dates and increased market competitiveness. Along with guaranteeing consistent adherence to industry standards for patient safety and product quality, the initiative strengthens compliance with FDA requirements. Additionally, by reducing waste and upholding lean manufacturing principles, the research improves resource utilization and supports operational sustainability within the biotechnology production environment. These contributions are crucial to boosting the biotechnology manufacturing industry's productivity, compliance, and sustainability.

Literature Review

This section will go into greater detail about the key topics that must be understood in order to comprehend the Cleaning Certification process. The topics that will be discussed are Manufacturing Execution System, Laboratory Information Management System, FDA Validation of Cleaning Processes (21 CFR 211.67), Lean Manufacturing, DMADV Methodology, and the Cleaning Certification Process.

Manufacturing Execution System (MES)

The MES is essential in the biotechnology manufacturing process to maintain transparency and control throughout the production lifecycle. It is a dynamic system that handles data, compliance, and operating standards rather than just a software program. MES makes it possible to make data-driven decisions, monitors production activities in

real-time, and interfaces with other systems like ERP and Quality Management. It guarantees adherence to the law, notably concerning Good Manufacturing Practices (GMP), while upholding regulatory standards and improving product quality and safety [1] [2].

Laboratory Information Management System (LIMS)

The foundation of contemporary laboratory operations, LIMS makes sample handling, data management, and regulatory compliance more manageable. With an emphasis on precision, effectiveness, and adherence to industry standards, it has developed to meet the needs of a changing scientific field. LIMS organizes samples, procedural guidelines, tools, and data analysis to improve data integrity and streamline laboratory procedures. While securing data for later analysis, interpretation, and reporting, it coordinates equipment and staff movements [3]. The dedication of laboratories to data integrity, quality, and operational excellence is exemplified through LIMS.

FDA Validation of Cleaning Processes (21 CFR 211.67)

Strict equipment cleaning and maintenance standards are laid forth in 21 CFR 211.67, the FDA's Validation of Cleaning Processes. It aims to prevent equipment malfunctions and contamination incidents that could jeopardize drug product safety, quality, and potency. Compliance with these regulations is essential for ensuring product quality, safety, and regulatory alignment in biotechnology manufacturing [4] [5]. This regulation underscores the industry's commitment to patient safety and product quality.

Clean-In-Place (CIP) Systems

CIP systems are essential for maintaining product quality, safety, and operational efficiency in biotechnology manufacturing. They go beyond microbial contamination prevention, efficiently removing contaminants like grit and organic matter. CIP systems use automated circuits to create specialized cleaning solutions and ensure thorough equipment cleaning. Properly executed CIP processes are vital for adhering to regulatory standards and protecting patient safety by eliminating pollutants and residues [6].

Lean Manufacturing

Lean Manufacturing principles focus on operational excellence, waste reduction, and value optimization in manufacturing processes. This philosophy identifies and addresses seven waste categories: overproduction, overprocessing, waiting, transportation, motion, defects, and inventory. By eliminating these wastes, Lean Manufacturing enhances efficiency and resource utilization [7]. It aligns with the intention to optimize value delivery to customers and improve operational efficiency in biotechnology manufacturing.

Figure 1
Types of Waste

DMADV Methodology

The DMADV methodology within Six Sigma is a structured framework for process improvement and innovation. It emphasizes the importance of setting clear project goals, data-driven analysis, meticulous design, and rigorous Verification. DMADV promotes productivity, excellence, and innovation in biotechnology production, guaranteeing that procedures and goods satisfy consumer demands and industry norms [8].

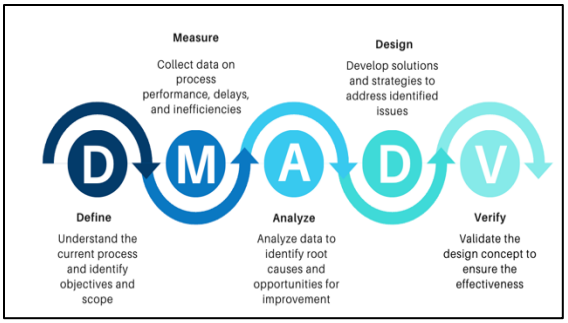


Figure 2
DMADV Methodology

Cleaning Certification Process

In biotechnology production, cleaning certification is a crucial step that guarantees patient safety and legal compliance. It entails careful cleaning techniques, adherence to SOPs, and equipment cleaning validation. MES and LIMS are essential for data management and reporting throughout the Cleaning Certification process. Maintaining product quality and safety requires compliance with FDA rules and industry standards [9] [10]. At the heart of this intricate procedure is the pivotal role played by the Manufacturing Execution System (MES). Within the Manufacturing Execution System (MES), the execution of batch records for product manufacturing takes center stage. These detailed batch records encompass crucial information regarding the equipment employed throughout the batch run. However, before any equipment is brought into service, it undergoes a meticulously orchestrated and automated Clean In Place (CIP) process, representing a pivotal facet of equipment cleaning and maintenance [10]. Central to the CIP process is the adherence to Standard Operating Procedures (SOPs), which meticulously document information about validated tanks and the specific solutions approved for use. These SOPs provide the essential guidance needed to navigate the intricate landscape of the cleaning process. Notably, if a particular equipment has been validated for a specific solution, it obviates the need for cleaning verification samples. Conversely, when equipment lacks validation for a given solution, a protocol is in place to take samples from various critical points during the CIP process [10]. Every cleaning that is made has a respective worksheet that documents the recipe, if samples were taken, and the identification of samples. This data can be found in the Manufacturing Execution System (MES) in the Equipment Log, where you can find worksheets by date using the reference of the batch run that comes after the cleaning.

The Laboratory Information Management System (LIMS) emerges as an indispensable cornerstone in the realm of data management within the manufacturing process. In this platform, the operator who made the sampling set the status of the samples as collected and delivered. After the testing in the Laboratory, through the Laboratory Information Management System (LIMS), the laboratory technician updates the results of each sample. When samples are approved, the system generates the report of each sample. After collecting all the data needed for the report, we fill out the Cleaning Certification report.

Figure 3
Steps for the Cleaning Certification Process

METHODOLOGY

The research methodology employed in this study is rooted in the DMADV (Define-Measure-Analyze-Design-Verify) approach, with a primary emphasis placed on the Design phase. This approach is a structured framework widely utilized for process improvement and optimization. In the context of this research, it serves as a robust framework to systematically address and enhance the Cleaning Certification process within the biotechnology manufacturing industry.

Table 2

DMADV Methodology

DMADV Methodology	
Phase	**Description**
Define	Understand the current process and identify objectives and scope.
Measure	Collect data on process performance, delays, and inefficiencies.
Analyze	Analyze data to identify root causes and opportunities for improvement.
Design	Develop solutions and strategies to address identified issues.
Verify	Validate the design concept to ensure its effectiveness.

- **Define phase:** The research's foundation is the Define phase, which focuses on thoroughly understanding the present Cleaning Certification procedure used in the biotechnology manufacturing industry. The current workflow is thoroughly examined to determine its complexities and problematic areas. The main aims are establishing precise objectives, defining the project's scope, and learning more about the process's difficulties. The research team gathers data from multiple sources to build a roadmap for later steps. The foundation for a systematic strategy to address and enhance the Cleaning Certification process is laid during this phase.
- **Measure phase:** The Measure phase builds on the Define phase by collecting extensive data about the inefficiencies and delays in the Cleaning Certification workflow. Data is acquired from various sources, including feedback from team members involved in the process directly and other performance measurements. The data collection method considers quantitative and qualitative elements to provide a comprehensive picture of the issues facing the current process. Important indicators like lead times and document handling times are painstakingly reviewed to build a solid dataset. This phase's findings are crucial for identifying areas that need improvement and, eventually, improving operational efficiency in the biotechnology manufacturing industry.
- **Analyze phase:** The research team must first analyze the data gathered to pinpoint the primary reasons for inefficiencies and delays in the Cleaning Certification process. This is a crucial stage. A thorough inquiry uses various techniques, such as statistical analysis and qualitative reviews. The overarching objective is to uncover profound insights into the contributing factors that underlie the identified challenges. This phase also prioritizes areas that show promise for optimization and streamlining. By identifying and prioritizing opportunities for improvement, the research team sets the stage for the subsequent steps, strategically aligning efforts to enhance operational efficiency within the biotechnology manufacturing sector.
- **Design phase:** The Design phase is at the heart of the research, where the focus shifts to developing an innovative digital platform tailored specifically for the Cleaning Certification process. This platform aims to seamlessly integrate the MES and LIMS, automating the Cleaning Certification process and expediting sample testing. The Define, Measure, and Analyze phases produce insights that guide the development process. The platform must be designed using user-centric design principles to ensure it meets the requirements and workflows of the individuals involved in Cleaning Certification. The creation of the platform heralds the start of a revolutionary era that strongly emphasizes real-time data accessibility and sharing while minimizing human verification and paper-based documentation.

- **Verify phase:** The research's final stage, the Verify phase, is distinguished by validating the design concept of the Cleaning Certification digital platform. The platform's usefulness, effectiveness, and capacity for quick sample processing. Precise testing methodologies ensure the platform meets and surpass efficiency and accuracy standards. The platform's design concept adaptability and practical effectiveness are provided via user feedback, essential in iterative refinement and optimization. This step establishes the platform's readiness to redefine operating rules, industry standards, and the Cleaning Certification procedure within the biotechnology manufacturing industry.

RESULTS AND DISCUSSION

Integrating a digital platform into the Cleaning Certification process has profoundly reshaped the biotechnology manufacturing industry. This section examines the results of this integration using the DMADV methodology, highlighting its substantial effects on efficiency, manufacturing procedures, and compliance with FDA regulations. It underscores how this transformative step has bolstered operational efficiency, optimized manufacturing workflows, and reinforced the industry's commitment to stringent regulatory standards.

Define

The project's scope and goals were defined during the Define phase, which also involved developing a thorough understanding of the current Cleaning Certification procedure. An essential issue with possible consequences for patient safety, product quality, and FDA compliance was highlighted as delays in sample testing. The foundation for methodically resolving these difficulties was laid during this phase.

Measure

In the Measure phase, detailed data was gathered, including records, process metrics, and feedback from team members. One of the Measure phase's central outcomes was quantifying delays in sample testing (*Tables 3, 4, and 5*). By quantifying the delays, the research project gained a clear picture of the inefficiencies within the process, enabling targeted interventions to enhance efficiency and timeliness. Also, a survey was conducted of eight persons who are part of the team that makes the Cleaning Certification Report to receive input and feedback about the Cleaning Certification process (*Figures 4, 5, and 6*). An analysis of resource usage revealed areas where paper-based documentation could be reduced and resource efficiency could be increased.

Table 3

Elapsed Time to Test and Approve Samples for Batch #1

Equipment ID	Sample ID	Delivered Date	Testing Date	Approved Date	Elapsed Dates
TK-1667-001	4093360 4093361	20-Apr-2023	30-May-2023	30-May-2023	40
TK-0611-001	4086572 4086573	16-Apr-2023	26-Apr-2023	26-Apr-2023	10
TK-0615-001	4094100 4094102	19-Apr-2023	17-May-2023	17-May-2023	28

Table 4

Elapsed Time to Test and Approve Samples for Batch #2

Equipment ID	Sample ID	Delivered Date	Testing Date	Approved Date	Elapsed Dates
TK-1667-001	4053654 4053658	02-Apr-2023	20-Apr-2023	20-Apr-2023	18
TK-0611-001	4049914 4049916	29-Mar-2023	16-Apr-2023	16-Apr-2023	18
TK-0615-001	4043659 4043660	27-Mar-2023	26-Apr-2023	26-Apr-2023	30

Table 5

Elapsed Time to Test and Approve Samples for Batch #3

Equipment ID	Sample ID	Delivered Date	Testing Date	Approved Date	Elapsed Dates
TK-1667-001	4043669 4043670	30-May-2023	07-Jun-2023	07-Jun-2023	8
TK-0611-001	4050978 4050979	19-Jun-2023	29-Jun-2023	29-Jun-2023	10
TK-0615-001	4050953 4050954	11-Jun-2023	26-Jun-2023	26-Jun-2023	15

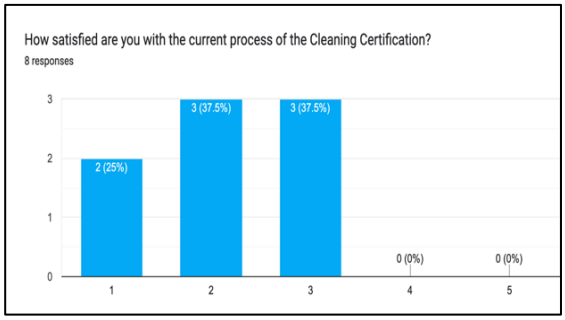


Figure 4

How Satisfied are You with the Current Process of the Cleaning Certification?

With this question, we wanted to know the satisfaction of the team that does the Cleaning Certification Report. The scale was from 1 to 5, with 1 as very unsatisfied to 5 as very satisfied. The votes were the following: 37.5% voted for 3 as neutral, 37.5% voted for 2 as unsatisfied and 25% voted for 1 as very unsatisfied.

The 100% of the team that does the Cleaning Certification Report responds that the Cleaning Certification Process needs to be improved.

Figure 5
Do You Think that the Cleaning Certification Process Needs to Improve?

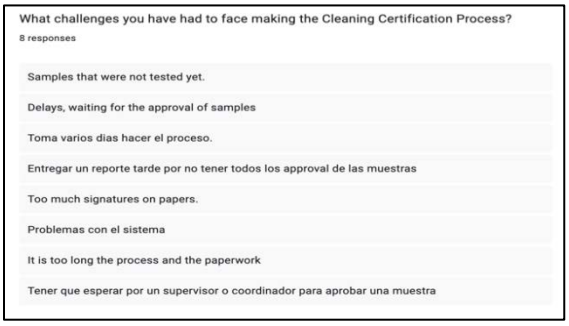


Figure 6
What Challenges You Had to Face Making the Cleaning Certification Process?

Analyze

Data analysis and qualitative assessments were used in the analysis phase to examine the fundamental reasons for inefficiency. Through the meticulous scrutiny of data and a comprehensive understanding of the root causes, specific areas with the most significant potential for enhancement were identified and systematically ranked in terms of their importance. For this reason, after making the survey, we identified the main problems that they were facing. There were mostly delayed samples and lengthy processing that sometimes caused late release to the batches, among others. This prioritization process ensured that subsequent efforts in the Design phase were strategically aligned with addressing the core issues, thereby maximizing the impact on operational efficiency within the biotechnology manufacturing industry.

In Figure 7, the current Cleaning Certification process could take up to three months to complete. Some causes are samples not tested, samples waiting for approval, and lengthy processing.

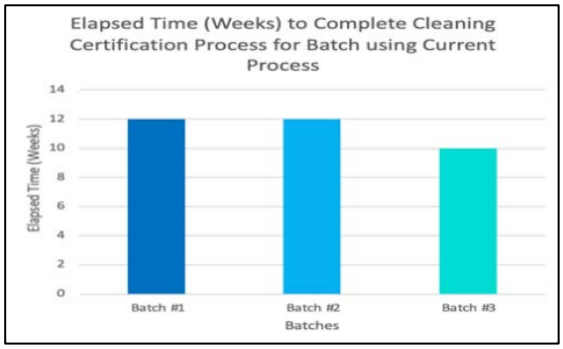


Figure 7
Graphic of Three Batches Elapsed Time in Weeks to Complete the Cleaning Certification Process Using the Current Process

In this graphic, can be seen three batches which have three samples each. The time that is in the graphic was calculated with the delivery date and the sample approval date. With this, we can see that the time that it takes to test and approve samples could take up to 40 days and an average of 19.66 days in these three batches.

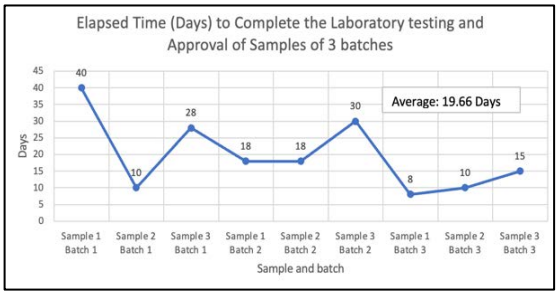


Figure 8
Graphic of Three Batches Samples Elapsed Time in Days to Complete the Laboratory Testing and Approval

Design

Automation techniques were implemented during the Design phase to speed up sample testing

and data sharing. To improve overall efficiency, centralized data integration was created to eliminate the necessity for numerous data sources. The platform's automated capabilities enable the seamless sample data transfer from the LIMS and the MES to bring up all batch information, cleaning worksheets, and equipment with their respective solution. Another feature that will be found is a notification-activated program, quality management ER, report management, and accessibility to find all the Standard Operating Procedures (SOP) that are used in the process. This strategic move significantly expedites the sample testing process and concurrently reduces the potential for errors associated with manual data entry.

Figure 9
Cleaning Certification Platform Home Page

Figure 10
Example of the Notifications Activated Program When a Sample is Delivered

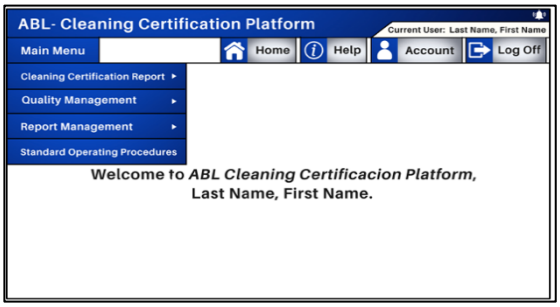


Figure 11
Home Page with the Different Options in the Main Menu

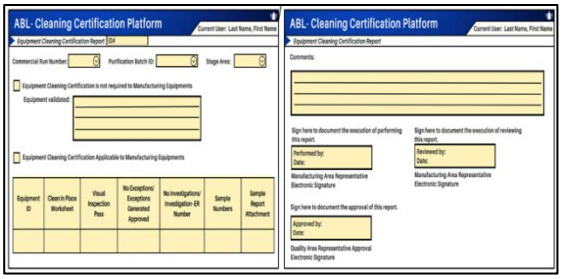


Figure 12
Example of How will Look the Cleaning Certification Report

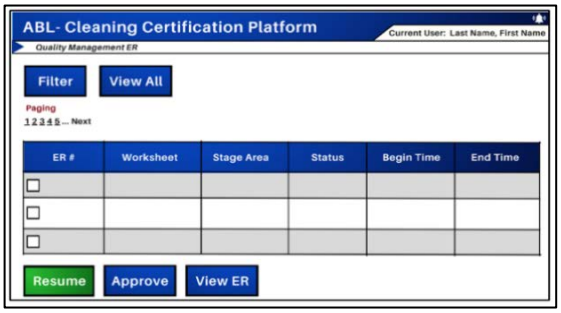


Figure 13
Quality Management ER Page

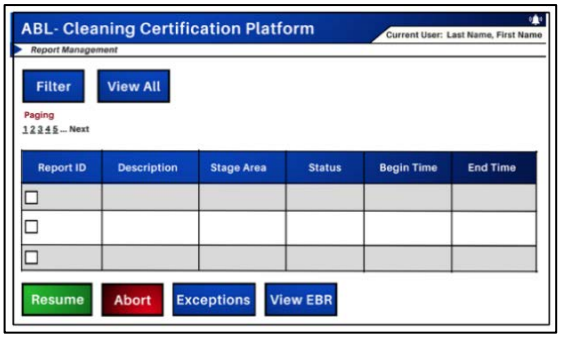


Figure 14
Report Management Page

Verify

The digital platform was verified to assure compliance with efficiency and accuracy requirements. User feedback integration emerged as another pivotal outcome. In this phase, user feedback played a central role in shaping the iterative refinement and optimization of the platform (*Figures 15, 16, and 17*). In these figures, it can be found the survey was created to get feedback and opinions. Actively soliciting and incorporating user insights ensured that the platform's design and functionality aligned seamlessly with the practical needs and workflows of personnel engaged in the Cleaning Certification process.

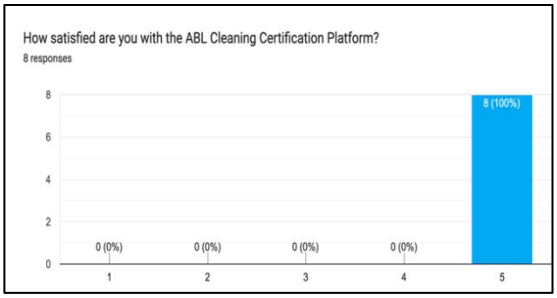


Figure 15
How Satisfied are You with the ABL Cleaning Certification Platform?

The 100% of the team that does the Cleaning Certification Report responds to their satisfaction with the new platform design concept.

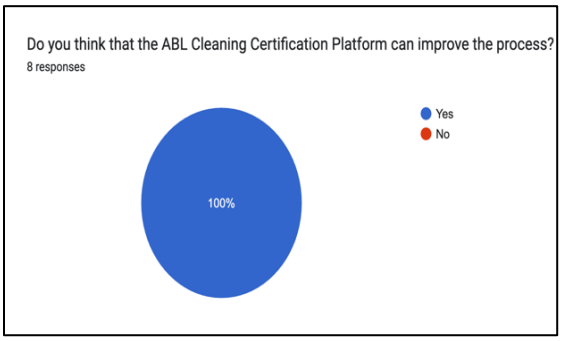


Figure 16
Do you Think that the ABL Cleaning Certification Platform can Improve the Process?

The 100% of the team that does the Cleaning Certification Report responds that the ABL Cleaning Certification Platform can improve the process.

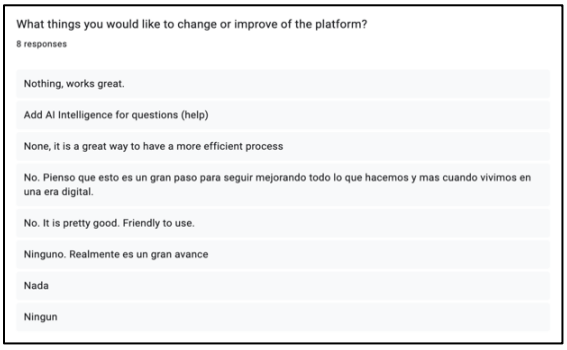


Figure 17
What Things You Would Like to Change or Improve of the Platform?

CONCLUSION

The Manufacturing Execution System (MES) and the Laboratory Information Management System (LIMS) are to be combined into a single digital platform to meet the difficulties a biotechnology manufacturing company faces in its Cleaning Certification procedure. This platform is in keeping with lean manufacturing principles to streamline the Cleaning Certification procedure and improve operational effectiveness. The expected results include increased adherence to FDA standards, faster process, shorter waiting times, and quicker sample testing—all of which will improve the operational environment. This program demonstrates the business' dedication to regulatory compliance, high-quality products, and patient safety.

Summary of Contributions

- Integrated Digital Platform: The project streamlines the formerly labor-intensive Cleaning Certification process by integrating Manufacturing Execution System (MES) and Laboratory Information Management System (LIMS) on a cutting-edge integrated digital platform.
- Efficiency Improvements: The project's success in increasing operational efficiency is evidenced by the project's possible reductions in sample testing delays and cleaning certification process.
- Compliance Adherence: The program ensures the highest patient safety and product quality standards while reinforcing compliance with FDA requirements.
- Resource Optimization: The initiative adheres to lean manufacturing principles, emphasizing resource efficiency and environmental sustainability by decreasing waste and manual interventions.
- Streamlined Workflow: The research radically alters the manufacturing operational dynamics of biotechnology, promoting a more efficient workflow.

Future Research

Research in the future may broaden the use of digital platforms in other facets of biotechnology

production, further automating tasks and improving productivity. Additionally, exploring the application of emerging technologies like artificial intelligence (A.I.) and machine learning (ML) in quality control and compliance checks promises to revolutionize the industry. These advancements will reinforce the sector's commitment to maintaining high-quality standards and embracing technological innovation.

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