Assay Report Documentation and Storage Process Improvement Using DMADV Methodology

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Abstract *— As part of the Process Engineering team, one of our goals is to identify areas with opportunities in our current manufacturing processes. It was identified an opportunity to improve the assay hard copy documentation generated in the Analytical Laboratory area because the reports are printed in hardcopy, and the audit process requires 3 signs in every paper. The assay hardcopy documentation and audit trail process will be changed to a paperless process following the Design for Six Sigma (DFSS) systematic approach and DMADV to reduce costs of the process, transforming the documentation repository in an electronic data base for the client convenience.*

Key Terms *— DMADV, Lean, Process Improvement, Six Sigma.*

PROBLEM STATEMENT INTRODUCTION

In an Analytical Laboratory (AL) located in a Manufacturing Building, the Analysts perform Protein Concentration assays in a daily basis, Protein Concentration assays are performed using a Variable Pathlength Fiber-Optic Spectrophotometry Technology instruments which are connected to a Computer System (CS) using a Software Application. Every assay performed, generates a report with the data sample measurements, graphics, regressions and results. The report is printed in Cleanroom paper and attached to another cleanroom paper, for every page of the assay reports requires signatures from two (2) Analyst as Perform and Verify and a third signature for Review from a Quality Assurance (QA) Associate, then the assay report is placed on a binder.

Research Description

This research has the mission to evaluate an existing assay report audit process using a systematic approach with the Process Improvement Methodologies that applies, where we can identify areas with opportunities for improvement, adding value to the company, eliminating wastes from the process and increase the customer satisfaction.

Research Objectives

This research has pursued the initiative to improve an existing process by identify unnecessary tasks with no value added, measure current process tasks, analyze the options for the ideal design and optimize the process into a paperless one.

Research Contributions

The research contribution has a direct and positive impact to the organization, a process improvement opportunity was identified and addressed to move into a paperless process. Environmentally and sustainable is a win-win by eliminating/reducing the needs of paper and maximizing the time to perform value added tasks.

LITERATURE REVIEW

Lean started as rigorous process thinking in manufacturing by the 1450s in the Arsenal in Venice, but the first person to truly integrate an entire production process was Henry Ford in 1913 by consistently interchangeable parts with standard work and moving conveyance to create what he called flow production within car fabrication. Another person who improves Lean was Kiichiro Toyoda by the 1930s and revisited the Fords

original thinking and invented the Toyota Production System, leading lean exemplar in the world and stands poised to become the largest automaker in the world in terms of overall sales. Lean thinking was described and distilled in five (5) principles by James P. Womack, Daniel Roos and Daniel T. Jones in 1990, the principles are:[1]

- Specify the value desire by the customer
- Identify the value stream for each product providing that value and challenge all of the wasted steps
- Make the product flow continuously through the remaining value-added steps
- Introduce pull between all steps where continuous flow is possible
- Manage toward perfection so that the number of steps and the amount of time and information needed to serve the customer continually falls

Lean is the process of optimize systems to reduce costs and improve efficiency by identifying and eliminating processes and product waste. Lean can be used to improve all kind of processes in every industry.

Reduce waste is one aspect of a Lean Organization, also Joseph M. Juran wrote "Reducing Waste Alone Is Not Lean" Eliminate waste from a manufacturing process sound simple but the identification is not commonly noticed. Toyota Production System (TPS) defines three (3) types of waste: [2]

- Muri or overburden – Muri is all the unreasonable work that management imposes on workers and machines because of poor organization
- Mura or unevenness – Mura focuses on implementing and eliminating fluctuation at the scheduling or operations level, such as quality and volume
- Muda or non-value-added work – Mura is discovered after the process is in place and is dealt with reactively rather than proactively with muri and mura.

The seven (7) Wastes of Lean and Non-Value adding process are:

- Transportation – Movement of product that does not add value
- Inventory – More materials, parts or products on hand than the customers' needs
- Motion – Unnecessary movement of people that does not add value
- Waiting – Idle time created when material, documentation, workers or equipment is not available or ready
- Overproduction – Producing more than the customer needs
- Over-Processing – Doing more work more than the expected
- Defects – Waste of correction includes additional work performed

Six Sigma and Lean Six Sigma (adds Lean tools to the basic methodology)

Are quality improvement methods with value added enhancements of computers and an increasing array of statistical and other software packages. Six Sigma or DMAIC steps and tools most often used with it. The DMAIC phase steps are: [2]

- Define – define the problem as clearly as one can in words
- Measure – the current level of performance and voice of the customers
- Analyze – collected data to determine the cause of the problem
- Improve – by selecting the right solutions to solve the problem
- Control – to hold the gains

Design for Six Sigma (DFSS)

The evolution of many lessons learned within the past of year has led to the development of DFSS. It is focused on creating new or modified designs that are capable of significantly higher levels of performance (Approaching Six Sigma). DMADV sequence is a design methodology applicable to developing new or revised products, services and processes. The steps in DFSS enable

one to understand the customer and their needs. The DMADV phase steps are: [2]

- Define – Provide the goals and direction to design a new process or product with development of a team charter
- Measure – collects and translates customer needs
- Analyze – understand the information collected from the Voice of the Customer (VOC) and define the design features that collectively will be developed into a concept and then into one or more high level designs
- Design – In this step, the final product or process designed is developed. A detailed designed with associated design elements is completed and the critical-to-process variables are defined
- Verify – The new designs plan is implemented, and the organization prepares for full-scale rollout and puts control mechanism in place.

21 CFR Part 11 Electronic Records and Electronic Signatures

In March of 1997, FDA issued final part 11 regulations that provide criteria for acceptance by FDA, under certain circumstances, of electronic records, electronic signatures, and handwritten signatures executed to electronic records as equivalent to paper records and handwritten signatures executed on paper. These regulations, which apply to all FDA program areas, were intended to permit the widest possible use of electronic technology, compatible with FDA's responsibility to protect the public health. [3]

- Data Integrity = State of a collection of data which needs to be complete, accurate and consistent across all the generation process until the archival.
- Electronic Record = combination of text, data and information representation, which is generated, modified, stored and retrievable by a Computer System (CS).
- Electronic Signature = Computer data combination of letters, number and symbols used by individual accounts to be the equivalent to a handwritten signature.

The FDA 21 CFR Part 11 is a synonym for Good Documentation Practices (GDP) for Electronic Data, where the data must be:

- Legible
- Contemporaneous with Time-date stamps
- Attributable (E-Signatures with accounts that have User Id and Password)
- Traceable
- Storage in a specified database location with controlled privileges according to the established user roles

Recording of Results Analyst Worksheet

General: The laboratory analysts record descriptive information pertaining to the sample, its handling in the laboratory, and analytical findings and observations on worksheets are part of the FDA requirements. General directions and considerations for completing these forms or electronic records include: [4]

- Sample information required for worksheets (hardcopy or electronic) are initiated upon receipt of the sample by the analyst.
- Raw data and observations are recorded directly on the worksheets as acquired, when handwriting worksheets, the writing will be in permanent black or blue ink, and must be legible, neat, and of adequate size to be easily read or photocopied. [4]

Electronically Entered Raw Data

Analysts may enter raw data and observations electronically using electronic worksheet templates or web applications in lieu of printed forms. Data and observations are recorded directly on these templates at the time they are observed. When data and observations are recorded electronically, laboratories take additional measures to protect integrity which may include the following:

- The analyst carefully reviews entries before saving and closing the file containing the entries.

- Once raw data is entered electronically, and the completed worksheet file closed, changes to effect corrections to entries are now traceable. (e.g., by initiated and dated strikeouts and additions.)
- The files containing raw data entries are identified in order to link them to the sample to maintain traceability. [4]

Instrument-Generated Reports and Charts

When instrument-generated reports are included in an analytical package, the report should provide information needed to interpret its graphic, tabular, or computation output, such as: absorbency measurements, peak areas, retention times, wavelength maximum and other characteristics used in the generation of results.

METHODOLOGY

The methodology used within the Project will be DMADV which is an aspect of Design for Six Sigma (DFSS) usually used for Process Improvements where we will collect data/information by performing interviews and a Kaizen event with the Subject Matter Experts (SMEs) from the functional areas that are directly related to manufacturing process and can be impacted somehow their processes/procedures and redesign the current process more robust. The data/information gathered will be detailed in systematic approach with the DMADV methodology which is divided in the following phases five (5) phases: Define, Measure, Analyze, Design, Validate/Verify.

- **1st Phase – Define:** In the Define Phase we are going to evaluate if there is an area with opportunity, define the goal for the improvement in order to formalize the Project Plan.

  Deliverables includes: Voice of the customer (VOC); Project Scope and Project Objective. Across this phase the following tools were used: Kaizen Meeting Section, and Project Charter.

- **2nd Phase – Measure:** In the Measure Phase, the intention is to understand the Voice of the Customer (VOC), identify our requirements and project an established baseline.

  Deliverables includes: Customer requirements and Functional requirements. Across this phase the following tools were used: Value Stream Map (VSM).

- **3rd Phase – Analyze:** In the Analyze Phase, we are going to analyze the data/information gathered from the previous phase, to select the design options that fits better for our processes taking in consideration the requirements.

  Deliverables includes: Generate design concepts; Select Best Fit Design and Validate with customer.

- **4th Phase – Design:** In the Design Phase, the goal is transforming the best fit designed selected in the Analyze Phase into a detailed one.

  Deliverables includes: Operational Definition of the detailed design; Function; Expected Performance; Failure Mode & Effect Analysis (FMEA); Complete design verification test

- **5th Phase – Validate:** In the Validate Phase, the objective will be to transfer the functioning designed process into the area.

  Deliverables includes: Execute Protocol generated for the process verification; Updated Documentation – Standard Operating Procedures; Execute Control Plan and provide hyper care in the process; Transition to operational owners and validate.

RESULTS AND DISCUSSION

During the 1st Phase (Define) a Project Charter (Refer to Figure 1) with brief and concise information was created to obtain the Endorsement in the Project Management Forum. The goal is to Transform the assay documentation and storage in into a paperless process.

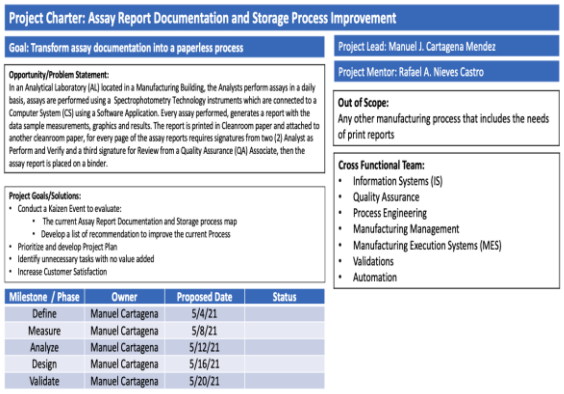


Figure 1
Project Charter

A Kaizen pre-work meeting section was conducted where the team discussed the Assay Report Documentation and Storage of the reports. During the Kaizen, the team:

- Create the current process in the Value Stream Map (Refer to Figure 2)

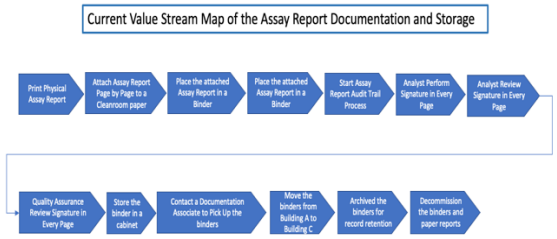


Figure 2
Current Value Stream Map (VSM)

The current Value Stream Map (VSM) demonstrates that the process definitely had an opportunity to improve the process by eliminating the hardcopy documentation which can leads the organization to be more environmental conscious and eliminating waste from the process.

The benefits will include:

- Man-Hour reduction
- Entry error reduction
- Paper cost avoidance
- Faster documentation completion
- Printer-Ink avoidance
- Printer Maintenance avoidance
- Binder-Paper decommission avoidance
- Audit Trail process time reduction
- Create space to storage other relevant/useful equipment's

During the **2nd Phase (Measure)** the Kaizen pre-work continues to collect data and feedback from the customer to explore the Assay Reports and Audit Trail documentation. The Value Stream Map (VSM) from the 1st Phase was updated by collecting the time and resources needed per task (Refer to Figure 3). The analyst who performs the assay use an analytical instrument which is connected to computer system (CS), software is actually configured to save the raw data generated during the assay in an electronic repository, however as per the standard operating procedure (SOP), they print the raw data in hard copy. The raw data hardcopy is then attached individually to a cleanroom paper, where the analyst who perform the assay made a cross-signature in every paper, in addition the assay hardcopy includes number of pages, performed and approve by signatures with date. To keep a traceability of these hardcopies, every binder includes a form which includes the information related to the test/batch with name and date/hour of the analyst who retrieve the form. In addition, the analysts from the laboratory already use the Manufacturing Execution Systems (MES) where they document the details about the instruments in use, instruments calibration date, batch information, assay testing number, etc. The Quality Assurance associates needs to be part of the audit trail review with the intend to verify the data remains accurate, contemporaneous and traceable, actually they perform the review in computes of the analytical laboratory and then they perform an exception comment in the Manufacturing Execution System which belongs to every assay to confirm the audit trail verification.

The team noticed that the opportunity is the gap that we have is to perform digital signatures regarding assay reports and audit trail, also the need of access to the folders where the raw data is storage. Also with the elimination/reduce of the need for assay hardcopy reports, the process will be improved.

The times documented in the Value Stream Map were an approximate of the time and resources that it takes to complete the task, another issue that

was bring to the Kaizen was the fact that the Assay Report Audit Trail evaluation needs to be executed in the Analytical Laboratory because the physical documentation and the Quality Assurance associates not necessarily will be in the laboratory at the moment when the Analyst finish their reviews, the Analysts needs to contact the Quality Assurance associates to inform that binders are ready for review.

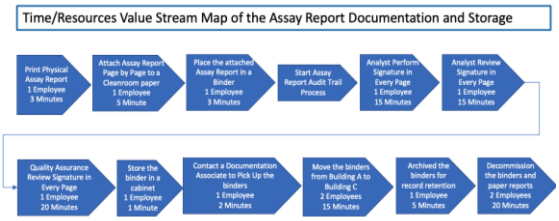


Figure 3
Time/Resources Current Value Stream Map (VSM)

The Value Stream Map (VSM) (Refer to Figure 3) shows that the Assay Report Documentation Process takes approximately 119 minutes, it can be divided in two phases:

- 1st Phase Print Report and Audit Trail Review = 79 Minutes
- 2nd Phase Transportation = 40 Minutes

Additional information from the Kaizen event:

- There is a limited space to storage binders
- The quantity of pages from an Assay Report will vary on the quantity of proteins included as part of the Assay, but as an average the quantity of papers needed per assay could be 75.
- Every binder is limited to storage 3 Assay Reports
- Documentation Resources are located in a different building than the Analytical Laboratory
- The price for a Cleanroom Pack (250 papers) is $25.00 ($0.10 each paper)
- The price per Binder is $10.00
- A daily average of 3 assays per day were executed during 2020 for a total of 1095 assays
- Approximately 82,195 papers were used during 2020, (82,195 papers x $0.10 = $8219.50)

Actions and customer needs:

- Eliminate/reduce the printing of physical Assay Reports
- Eliminate transportation of physical documentation
- Create storage space for more equipment/materials in the Analytical Lab
- Eliminate idle time created due to physical documentation
- Design where the reviews can be performed with digital signature
- Electronic Data Base with access

During the **3rd Phase (Analyze)** the team had the objective to use the information gathered during the 2nd Phase (Measure) to generate design concepts, evaluate design concepts and select the best concept in a high level that meet the functional requirements from the regulatory agencies and also meet the customer requirements.

To generate design concepts using a systematic approach, the team decide to use the SCAMPER technique which stands for:

- **S**ubstitute
- **C**ombine
- **A**dapt
- **M**odify
- **P**ut to another use
- **E**liminate (or Minify)
- **R**earrange (or Reverse)

What can I **Substitute** in the currently Assay Report Documentation and Storage Process?

- The assay report hardcopies can be substituted with electronic files.
- The signatures in the hardcopies could be substitute with electronic signatures.
- The storage space in the documentation building could be substituted with a specified database location.

What can I **Combine** in the currently Assay Report Documentation and Storage Process?

- The current Assay Report Documentation (Hardcopy) and Storage Process could be combined as a second option backup plan.

What can I **Adapt** in the currently Assay Report Documentation and Storage Process?

- The Standard Operating Procedure (SOP) used within the process could adapt instructions for the new process scenarios (Paperless) and the current process (Hardcopies).
- The privilege access of the associates which needs to access the folder where the Assay Report are storage could be adapted.
- The Manufacturing Execution System (MES) designs where the Analysts and the Quality Assurance associates documents data and information about the batch-assay that are working with could be adapted to fit the new process expectations

What can I **Modify** in the currently Assay Report Documentation and Storage Process?

- The process to perform the signatures in the Assay Reports and Audit Trail could be modified from manual signatures to electronic signatures.
- Paper inventory will be lower due to the modification of the paperless process.

What can I **Put to other use** in the currently Assay Report Documentation and Storage Process?

- The space used in the Analytical Laboratory to storage the binders with the hardcopies could be used to storage new instruments and/or consumables used in the area.
- The space used in the Documents Management building to storage the binders with the hardcopies could be put to other use.

What can I **Eliminate or Minimize** in the currently Assay Report Documentation and Storage Process?

- The needs of assay report hardcopies could be eliminated by implementing electronic signatures.
- The needs from the Quality Assurance (QA) associates to do the audit trail review in the Analytical Laboratory with the hardcopy reports could be eliminate by providing privileges in the specific database location where the assay reports are stored with a view access only.
- The binder/paper decommission could eliminated.
- The transportation of the binders could eliminate with the paperless process.

What can I **Rearrange** in the currently Assay Report Documentation and Storage Process?

- There were no opportunities identified to rearrange the current process because the intend within the project is to eliminate steps.

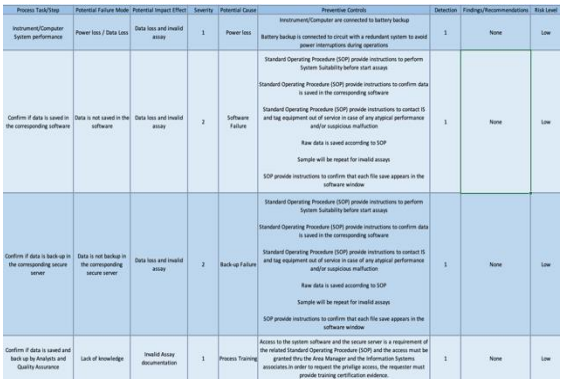
During the **4th Phase (Design)** the team had the objective to convert the brainstorming design collected during the 3rd Phase (Analyze) into a detailed one with the optimization functional design which can meet the customer, processes and business expectations.

The previous activities where the team collect data, brainstorm ideas and the Voice of the Customer (VOC) feedback, confirms that our Variable Pathlength Fiber-Optic Spectrophotometry Technology instruments had the capacity thru the Computer System (CS) Software Application to save the raw data reports generated from every Assay perform and that the data is actually saved in an electronic storage server.

Based on that research about that the raw data is stored and could be accessed by the employees that have access to the storage path we are going perform the design taking in consideration the Failure Mode and Effect Analysis (FMEA) (Figure 4) which is a systematic tool to identify the effects of a process failure and to eliminate and/or reduce the possibility of future failures. Since we are working to improve the current process, in addition we also focus on the prevention of failures.

The list with all the Quality Assurance Associates who works and provide support in Analytical Laboratory was completed with the intend to provide the “read only” privilege so they can access the storage server folder where the raw data and the audit trail of every assay executed will be available to access them from any area they were, all they need is a computer which is logged

with their credentials, with the access to the reports from their computers it will provide agility to the new process design.



Process Task/Step	Potential Failure Mode	Potential Impact Effect	Severity	Potential Cause	Preventive Controls	Detection	Findings/Recommendations	Risk Level
Instrument/Computer System performance	Power loss / Data Loss	Data loss and invalid assay	1	Power loss	Innstrument/Computer are connected to battery backup Battery backup is connected to circuit with a redundant system to avoid power interruptions during operations	1	None	Low
Confirm if data is saved in the corresponding software	Data is not saved in the software	Data loss and invalid assay	2	Software Failure	Standard Operating Procedure (SOP) provide instructions to perform System Suitability before start assays Standard Operating Procedure (SOP) provide instructions to confirm data is saved in the corresponding software Standard Operating Procedure (SOP) provide instructions to contact IS and tag equipment out of service in case of any atypical performance and/or suspicious malfuction Raw data is saved according to SOP Sample will be repeat for invalid assays SOP provide instructions to confirm that each file save appears in the software window	1	None	Low
Confirm if data is back-up in the corrsponding secure server	Data is not backup in the corresponding secure server	Data loss and invalid assay	2	Back-up Failure	Standard Operating Procedure (SOP) provide instructions to perform System Suitability before start assays Standard Operating Procedure (SOP) provide instructions to confirm data is saved in the corresponding software Standard Operating Procedure (SOP) provide instructions to contact IS and tag equipment out of service in case of any atypical performance and/or suspicious malfuction Raw data is saved according to SOP Sample will be repeat for invalid assays SOP provide instructions to confirm that each file save appears in the software window	1	None	Low
Confirm if data is saved and back up by Analysts and Quality Assurance	Lack of knowledge	Invalid Assay documentation	1	Process Training	Access to the system software and the secure server is a requirement of the related Standard Operating Procedure (SOP) and the access must be granted thru the Area Manager and the Information Systems associates.In order to request the privilige access, the requester must provide training certification evidence.	1	None	Low

Figure 4
Failure Mode and Effect Analysis

As part of the design, the Standard Operating Procedure (SOP) which is used as part of the Assays performed in the Analytical Laboratory will be revised with the redlines identified during the previous phase and will be reviewed and will remain in "Approved" status during this Validate phase. The current tasks to print the hardcopy assay report, attach the report to cleanroom paper, attached them in a binder, all the manually signatures in every page and the storage documentation in the building for hardcopy building retention will be part of the Standard Operating Procedure but it will be identified to be used only as a backup plan in case the network connection is down and as per need to continue operations it can be used.

New instructions will be included for the Laboratory Analysts and the Quality Assurance Associates in the Standard Operating Procedure to save the reports and raw data from the Software in the Computer System, with instructions to perform electronic signatures in the corresponding Manufacturing Execution System (MES), the information needed to identify the assay with the batch, date and hour when was executed, the storage server folder that was need to access in order to find the Assay Reports to perform the Audit Trail Process and the tasks with the instructions to provide the electronic signatures.

The new design (Refer to Figure 5) was run in MES using a Draft Protocol with the requirements of the test configuration before to move to last phase for validate the design. The test was successful by running an assay testing, saving the report, accessing the storage server folder and then performing the electronic signatures in the Manufacturing Execution System.

Figure 5
New Design Value Stream Map (VSM)

During the **5th Phase (Validate)** the team had the objective to transfer the completed functional design process to the Analytical Laboratory team.

At this phase the team identified:

- The areas with improvement opportunity
- The customer/business requirements
- The ideal design
- The risk within the assay process
- Process instructions for the new assay process design

An Approved Protocol was generated to run a validation exercise with the intend to cover the customer/business requirements as establish in the previous phases. To run the validation protocol, it is needed to schedule a window with the upper management to run the validation exercise during a slowdown and not be in use for commercial operations. The window needed will be five (5) days, the days will be distributed to perform an image of image of the computer systems, execute the protocol, complete and review the documentation and then the release of the equipment.

The protocol will include tests to cover all the identified risks during the Failure Mode & Effect

Analysis. In addition, a validation summary report will be performed as part of the requirements.

Updated Standard Operating Procedures (SOPs), the Manufacturing Execution Systems (MES) will be effective within the Protocol and Validation Summary Report effectiveness confirmation. It was accorded to provide hyper care from the Subject Matter Expert (SME) to the Analysts and Quality Assurance associates during the first week of the design implementation in the Analytical Laboratory in case any doubt and/or issue is presented.

CONCLUSION

The Assay Report Documentation and Storage Process was improved by using the DMADV Methodology by validating a paperless process design, the hardcopy reports were included in the Standard Operating Procedure as 2nd backup option but with our current process controls the expectation is to run paperless with a time reduction of approximately 10 minutes per assay by eliminating the needs to print the hard copies, 50 minutes to transport the binders to the documentation building. In addition, the new design provides flexibility and agility to the Quality Assurance associates to perform the audit trail process from every room in the building because of the easy access to the report in the secure server and the Manufacturing Execution System to perform the electronic signature. An approximate cost saving in paper of $8219.50 was achieved.

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