

Implementation of an alternate single use system used to store buffer solutions of Product X

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Abstract — *This research project was focused on the implementation of an alternate material used in the preparation of buffers of the production for Product X in a biotechnology company. Buffers are solutions that can resist pH change upon the addition of acidic or basic components, and their major role is to stabilize the pH of living systems. Due to the constant changes in the market because of the COVID-19 pandemic, the identified alternate material was implemented using the DMAIC methodology. This project pursues mitigating the cost increase of the primary material, but mostly it will secure the business continuity of Product X.*

Key Terms — *alternate material, biotechnology, buffer, DMAIC*

INTRODUCTION

The biotechnology industry has been affected by the constant changes on the market of raw materials because of the new reality associated to the COVID-19 pandemic. The main objective of biotechnology companies is to always secure the delivery of products to patients while maintaining high quality. Therefore, identification of alternate materials to address the unexpected cost increase or shortages in the raw materials market became an imperative to secure the delivery of the products to patients.

PROBLEM STATEMENT

The cost increase or scarcity of raw materials puts product supply at risk. The goal is to reduce the impact because of the primary material cost increment, comply with the 2022 production schedule, and secure delivery of Product X.

RESEARCH DESCRIPTION

The purpose of this project is to identify the path to follow to be able to implement the alternate material for the buffers needed on the production of Product X.

Research Objectives

The project aims to implement an alternative to the material used in the production of buffers for the production of Product X by May 30, 2022.

Research Contributions

The main contribution of the project is to secure business continuity and on-time delivery of Product X.

LITERATURE REVIEW

Puerto Rico is considered the number-one bioscience manufacturing hub in the US and has more than 30 years of excellence in sterile manufacturing. The principal companies are medical device manufacturers and pharmaceutical and biotechnology industries [1]. A biotechnology company is an industry that produces medicine derived from living organisms. Some applications of biotechnology are antibiotic production, restriction enzymes, protein production and eukaryotic viruses [2]. A general biologics workflow for pharmaceutical and biotech manufacturing is presented below [3]:

- Production cell line
- Cell culture
- Expansion of cells (fermentation)
- Cell harvested
- Extraction of the product with specific chemical steps
- Formulation stage
- Filling to specific configuration (vials, syringes, or cassettes)

- Product is stored on proper temperature
- Product delivered to the consumer

Focusing on the buffer exchange stage, buffers are solutions that can resist pH change upon the addition of acidic or basic components, and their major role is to stabilize pH of living systems [4].

Due to the pandemic that the world is still living through since 2019, the global market has been affected. End-to-end impact to Supply Chain was observed from material shortage, increase of cost, and difficulties on transportation results of companies limiting their inventory levels.

The White House’s official webpage describes that shortage and supply-chain disruptions are significant, but most of the time transitory [5]. Figure 1 shows the supply chain disruptions by sector. The manufacturing sectors takes the first place. Demand is increasing and industries present cascading issues regarding the supply-chain that cause shortages and abrupt price increases. At the same time, this material affects consumer prices.

Some disruptions in the industries may be caused by unexpected strong demand with low inventory levels, supply shock due by failure, or natural disasters.

One way that manufacturing companies try to mitigate abrupt supply chain changes is to build safe inventory levels. At the same time, they identify materials that have experienced significant market changes and identify alternative materials for them. The incorporation of the alternate material on the process helps industries comply with their demands and secure business continuity and on-time delivery.

General Concepts of DMAIC Methodology

[6] defines DMAIC as a problem-solving methodology used to improve processes. The acronym stands for Define, Measure, Analyze, Improve, and Control for the specific problem. The methodology can be used for product or service Lean Six Sigma projects to comply with the outcomes and benefits expected.



Figure 1
Supply chain disruptions by sector

- **Define:** Focuses on understanding who the customer is, their requirements and expectations, and the core business process involved with project boundaries.
- **Measure:** Focuses on the extent of the issue by quantifying it with different techniques. These techniques can be divided into four main categories: process analysis, data collection, measurement systems, and process capability analysis.
- **Analyze:** This step entails data collecting and process mapping in order to identify root causes of faults and areas for improvement. It also identifies performance gaps between present and desired performance, as well as objective statistical processes and confidence limitations.
- **Improve:** This stage focuses on improving the target process by coming up with innovative ways to solve and prevent difficulties.
- **Control:** Focuses on regulating improvements in order to keep the process on track and avoid reverting to the "old ways." Simultaneously, it creates a continuous monitoring plan by institutionalizing the improvements made through system changes.
- **VOC:** [6] defines the Voice of the Customer (VoC) as “a way to listen to the customer’s needs and perceptions.” This is a critical step for any project and must have a detailed plan to gather and collect feedback.
- **Fishbone diagram:** Also known as a Cause-and-effect diagram, it identifies the problem statement and potential contributing factors divided into categories.

The tools to be used in the upcoming project stages will be determined based on the outcomes of the Define stage and the progress and needs of the project.

RESULTS AND DISCUSSION

Smartsheet was used to maintain the overall tracking of the project and provide visibility to all the supporting functional areas. Smartsheet is a software that facilitates team collaboration, workflow automation, content management, and governance administration (figure 2).



Figure 2
Smartsheet dashboard example

Then, a project outline was created to describe the steps to follow and have an overall visibility of the project lifecycle (figure 3).

During the path of the project, the following assessments and results were obtained.

Project Methodology

Due to the limited time available to implement the project, only a few tools from the DMAIC methodology were used.

For the “Define” stage, the following tools were used:

- **Project charter:** A document that outlines the why, what, how, and who of the project to be discussed with team members and stakeholders
- **SIPOC:** A tool used before the work or project begins to identify all the important elements of the improvements. SIPOC takes into account the suppliers, inputs, improvement process, outputs, and customers. Finally, it is always recommended to display the SIPOC diagram visible for all the team members to see (chart, transparency, or a wall in an identified area) and discuss with the project sponsor, champion, and stakeholders involved.

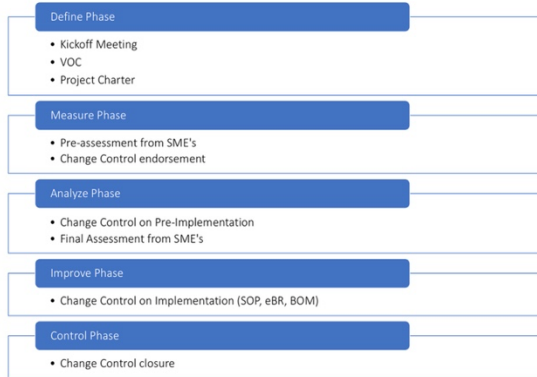


Figure 3
Project outline

On the Define phase, first, a VoC was made to understand the business's needs and the scope and expected outcome of the project. Then, a cross-functional kickoff meeting was carried out to understand the affected areas and the modifications and actions to be addressed, and to receive feedback from the Subject Matter Experts (SMEs).

The next step required the creation of a fishbone diagram to see the factors that may affect the production of Product X (figure 4). For the initiative,

the fishbone diagram was focused on the Materials section, specifically on shortage and cost.

Then, a project charter was developed in collaboration with the SMEs and Quality representatives (figure 5).

On Measure, pre-assessments were requested from the different functional areas and the tasks that may need to be completed as part of the project were identified. The following functional areas provided assessments: Quality, Manufacturing, Process Development (product and process), Risk Management, Product Devices, Environmental Health and Safety (EHS), Regulatory, Partner Client, and Training. These pre-assessments, along with the Project Charter, were used to present the project in the Change Control Review Board. Both Manufacturing and Quality management endorsed the project, which enabled the initiation of a change control record.

On the Analyze stage, the pre-assessments were formalized by each of the functional area SMEs and documented in the change record. Then, the record was promoted to the pre-implementation phase.

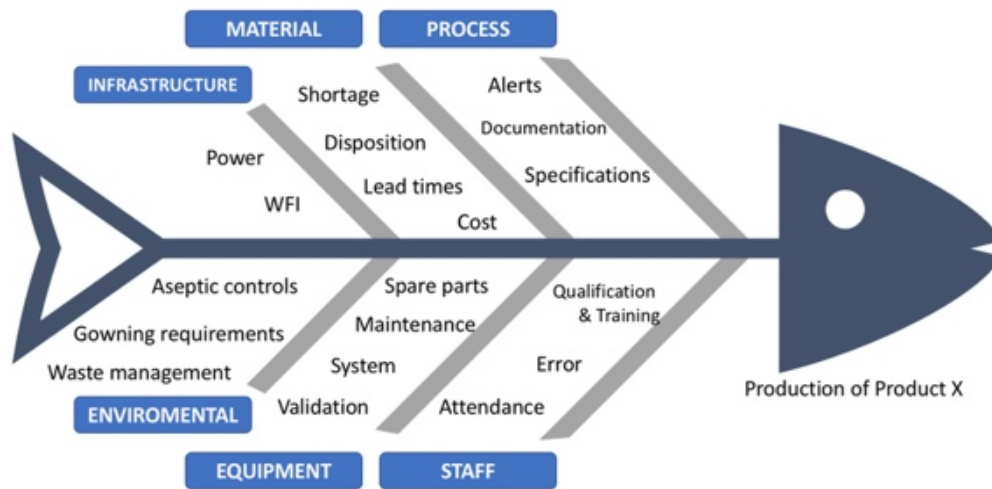


Figure 4
Fishbone diagram of Product X production

Project Title		Addition of an alternate material used for the preparation of buffers of the production of Product X		Project Manager		Juleika Villarrubia	
Start Date		03/01/2022		End Date		05/30/2022	
				Project Sponsor		Esteban Rivera	
Business Need							
Is needed the addition of an alternate material used the preparation of buffers of the production of Product X. This addition will mitigate the increase of cost of the primary material due to COVID-19 pandemic, but most importantly it will secure the business continuity of Product X.							
Project Scope				Goal			
In-Scope		Buffers of Product X		Out-Scope		Other products and buffers	
Achieve the addition of alternate material before May 30, 2022							
Risk and Issues				Assumption and Dependencies			
Time constrain of implementation							
No assumptions							
Financial Impact				Team Members			
Business continuity							
Manufacturing staff, Manufacturing Management, Process Owner, System Owner, Quality representative, Engineering SME, Process Development SME							
Milestones and Deliverables				Resources Required			
Change Control endorsement, Final Assessments completed, Material movement assessment							
Special cart for the movement of alternate material							

Figure 5
Project charter

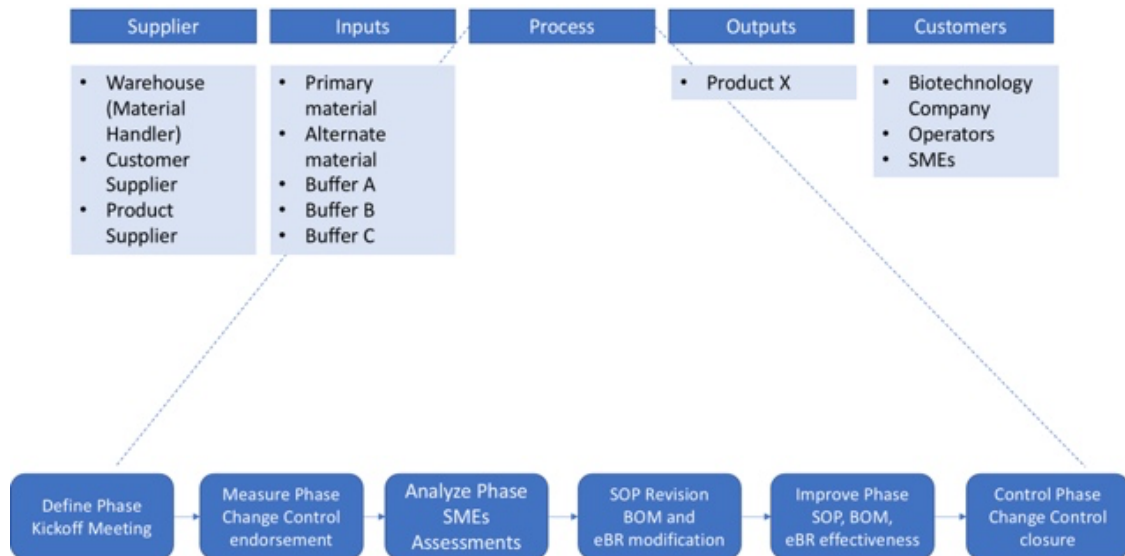


Figure 6
SIPOC Diagram of the project

During the Improve stage, the team will perform the modification needed to include the alternate material in the Bill of Materials (BOM), Standard Operating Procedures (SOPs), and Electronic Batch Record (eBR). The Standard Operating Procedure (SOP) is a detailed document that includes step-by-step sequence directions, cautions, and precautions to consider throughout the process. In addition, the document considers all the industry regulations, provincial laws, or own standards for running the business and complying with the customer's needs. The electronic batch record (eBR) is a computerized

record of all the important operations in the creation of each product batch, whether entered manually or electronically. Some of the information included for each batch are the operators who executed the actions, the manufacturing process, equipment, material, and supplies used.

These procedures must be revised by the SMEs and verified for quality until they are effective. It is important to have a scheduler representative to understand what is the best moment to make the changes without affecting the schedule of the manufacturing area. This action will complete the

implementation of the project and will mitigate the possibility of supply interruption.

Finally, on the Control phase, it is expected to finish documenting the record until its closure. In addition, after the completion, a gap assessment will be performed with the manufacturing area and sponsor to understand if a new area of opportunity is identified and to validate the accuracy of the Define phase.

CONCLUSION

This project led us to construct a path to implement the alternative material used in the production of buffers for the production of Product X by May 30, 2022. By carrying out the DMAIC methodology, the VoC understood the importance of the change to secure business continuity and on-time delivery. Modification of the SOP, eBR, and BOM for the incorporation of the alternate material will be completed in time to comply with the implementation date of May 30, 2022.

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