Simplification of the Weighing Process in the Raw Material Dispensing Unit

Krisalys Rios Bosques
Master's in Engineering Management
Héctor J. Cruzado
Graduate School
Polytechnic University of Puerto Rico

Abstract *— The weighing of excipients on the Rapid Material Unit for buffer formulation takes too long to be completed. The leading causes of this problem are the need for more standardization throughout the process, the inefficient distribution of excipients, and the lack of training for manufacturing personnel. The weighing process was studied to reduce the time it takes to complete a weight campaign. It was found that by creating a new design structure for the fragmentation and adding the instructions to the operational documents, 3.15 hours were reduced, enabling the process to become more agile, therefore increasing its productivity.*

Key Terms *— aseptic processing, simplification, pharmaceutical, weighing*

INTRODUCTION

Headquartered in Titusville, New Jersey, Janssen Pharmaceuticals is named after Dr. Paul Janssen, a leading pharmaceutical researcher, pharmacologist, and general practitioner. Janssen Pharmaceuticals joined the Johnson & Johnson family of companies in 1961. The company has grown over the years to serve the changing needs of patients and the healthcare industry. As a leading pharmaceutical company in the United States, the focus is on innovation on some of the most devastating diseases and complex medical challenges across six therapeutic areas: cardiovascular and metabolism, immunology, infectious diseases and vaccines, neuroscience, oncology, and pulmonary hypertension.

Janssen has had a location in Gurabo, Puerto Rico, for 40 years, having at least 800 hundred employees. Janssen is divided into two major areas: Solid Molecule (SM) and Large Molecule (LM) business units. SM focuses on pill manufacturing, and LM on biologics manufacturing.

The project was developed in the Large Molecule Business Unit or Parent. Currently, Parent has two main products: Remicade and Spravato. The project will focus on the first one, Remicade, specifically on the Rapid Material Dispensing Unit (RMDU).

The RMDU area is where Remicade's manufacturing starts, where all the excipients (sucrose, monobasic and dibasic) are weighted for buffer formulation. Currently, the weighing process is carried out in campaigns (five batches in one weight).

One batch consists of sucrose (38,000 g) in six containers, monobasic (167.3 g) in 3 containers, and dibasic (463.6 g) in three containers. For each campaign, 30 disposable containers are used; monobasic and dibasic containers cannot be reused. It was identified that the weighing process takes approximately 12 hrs. to be completed (9.4 hrs. weighting excipients and 3 hrs. in documentation). Therefore, the project's scope was focused on the weighing process, and its goal was to reduce from 12 containers to eight. The expected future state would consist of five containers to weigh sucrose (38,000 g), one for monobasic (167.3 g), and two for dibasic (463.6 g).

OBJECTIVES

The objectives of this project are to:

- Reduce weight processing time by 31% by implementing a new distribution of excipients in stainless steel containers.
- Reduce container waste generated in the weighing process by 50% using a new distribution of excipients.

- Reduce data entries by 25% in the weighing process, operational procedures, and forms.

BACKGROUND

Biopharmaceuticals are medications created using biotechnology. The fundamental distinction between these pharmaceuticals and other drugs is that they are not derived from natural sources and are synthesized through chemical processes. Companies that produce this type of drug are considered to follow aseptic processing. Aseptic processing is a manufacturing method that creates a bacteria-absent-free product without the requirement of submitting it to terminal sterilization processes [1].

The manufacturing of Remicade has been very complex since the beginning. Remicade is the commercial name of the product manufactured by Janssen Pharmaceuticals. The active ingredient in Remicade is infliximab, produced by a recombinant cell line cultured by continuous perfusion and purified by a series of steps that includes measures to inactivate and remove viruses [2]. Remicade is provided as a sterile, white, lyophilized powder for intravenous infusion. The pH is roughly 7.2 after reconstitution with 10 mL of Sterile Water for Injection, USP. Infliximab 100 mg, dibasic sodium phosphate dihydrate 6.1 mg, monobasic sodium phosphate monohydrate 2.2 mg, polysorbate 80 0.5 mg, and sugar are all present in each single-dose vial (500 mg) [2].

Since the product's formulation is complex, it is essential to assess the process to identify potential areas of improvement. Simplifying the weighing process for the excipients mentioned above could benefit all the manufacturing of Remicade because weighing is the first step in the process. Streamlining activities and duties while preserving or improving an operation's productivity may increase client and employee satisfaction due to quicker on-time deliveries and more efficient performance of processes [3]. This initiative will support the project's goal of increasing employee productivity and equipment utilization through process simplification.

Process simplification is a powerful tool in the Toyota Production System (TPS) and Standard Work. Standard Work is a tool that involves finding the best method of doing a process and making it the only way possible to do the process operation [4]. Having a standard work is a way of simplifying a process because the workforce will perform the activity following a standard.

METHODOLOGY

To improve the weighing process in the RMDU, it is essential to consider the activities carried out, the average performance time, and so on. It is necessary, as well, to determine if the current resource utilization is adequate so the system runs as expected. DMAIC Methodology, a data-driven quality strategy intended to improve processes [5], was used for this study. The structure of DMAIC encourages creative thinking within boundaries, such as keeping basic techniques, products, or services. DMAIC is the acronym for Define, Measure, Analyze, Improve, and Control.

RESULTS

Define Phase

The define phase, as the initial process of the project, seeks to outline the problem, find opportunities for improvement, state project goals, and establish an implementation plan. This phase is primarily supplemented by a Project Charter (see Figure 1) to define the improvement team's focus, scope, direction, and motivation [5].

The project's main objective is to reduce the containers used for the weighing process. One batch consists of sucrose (38,000 g) in six containers, monobasic (167.3 g) in three containers, and dibasic (463.6 g) in three containers (refer to Table 1). For each campaign, 30 disposable containers are used; monobasic and dibasic containers cannot be reused. It was identified that the weighing process takes approximately 12 hrs. to be completed (9.4 hrs.

weighting excipients and 3 hrs. in documentation). Therefore, the project's scope was focused on the weighing process, and its goal was to reduce from 12 containers to 8.

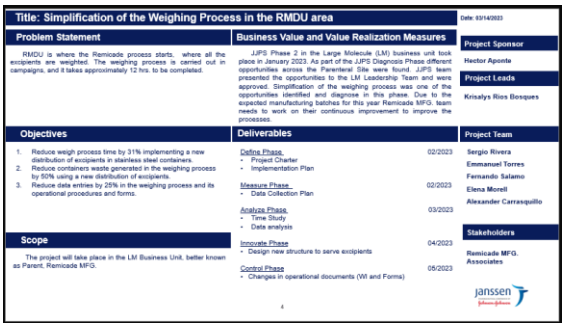

Figure 1
Project Charter

Table 1
Fragmentation Maximum per excipient

Excipient	Fragmentation Maximum	Container weight per batch
Sucrose	30	Five containers of 7,000 g One container of 3,000 g
Monobasic	15	Two containers of 61.6 g One container of 44.0 g
Dibasic	15	Two containers of 170.8 g One container of 122.0 g

As part of the defining phase, an implementation plan was developed for the project (refer to Table 2). An implementation plan is a detailed, step-by-step recipe for completing a task, process, or business objective [6].

Table 2
Implementation Plan

Activities	Date	Progress
Identify and diagnose opportunities in the RMDU	February 2023	Completed
Design Project Charter	February 2023	Completed
Execute time study in the weighing process	March 2023	Completed
Design fragmentation structure	February 2023	Completed
Calculate benefits (financial, EHS, data entries)	March 2023	Completed
Change to operational procedures (WI and FRM)	March 2023	Completed
Implementation	April 2023	Completed
Benefits confirmation	May 2023	Completed

Measure Phase

After defining the project, the measurement phase was next. The goal of the stage is to point out the opportunity as precisely as the team can. This phase is essential because the current state is understood, and data is collected to resolve the problem.

A data collection plan was developed to identify the tools and parameters to solve the problem. It was decided that a time study needed to be performed to understand how long an associate takes to complete a weighing in the RMDU. The study was conducted in March 2023 during the first shift, where two associates were selected for shadowing. As part of the study, average, normal, and standard times were calculated for the process. An allowance of 5% was given for each computed time. A sample size of 10 for each excipient weighted was obtained.

Analysis Phase

The analysis phase allowed the identification of the causes of variations and process wastes [5]. The identified causes formed part of the solution presented in the next step. As part of the study, average, normal, and standard times were calculated for each excipient weighed for the buffer formulation. The average time it takes for a worker to complete an individual task from start to finish [7] is calculated with the following equation:

$$avg = \frac{x1+x2+x3+x4+....}{n} \quad (1)$$

Normal time is a calculation that multiplies the average time by the rating factor, a metric that records the abnormal standards of a task. The rating system considers employee skill, effort, and consistency [7]. Normal time is calculated with the following equation:

$$normal = (avg) * (rating\ factor/100) \quad (2)$$

The standard time is when it takes a regular worker to complete a task under everyday conditions. It also considers different allowances, like unplanned breaks or unexpected delays [7].

Standard can be estimated with the following equation:

$$std = (normal) * (1 - allowance) \quad (3)$$

The time study performed in the RMDU area helped to understand how long it takes to complete the weight for one batch (refer to Table 3). It was concluded that weighing the three excipients takes 1.91 hrs. per lot. Since the weighing is carried out in campaigns (five batches), the total time for a campaign is 9.55 hrs.

Table 3
Time Study Results (in minutes)

Excipient	Average Time	Normal Time	Standard Time
Sucrose	63.50	66.68	63.34
Monobasic	29.40	30.87	29.33
Dibasic	21.80	22.89	21.75

Improve Phase

This phase helps to provide solutions to the problem statement of the project; a new fragmentation structure was developed to reduce the number of containers for weighing. The new fragmentation structure for one batch consists of five containers of sucrose, one monobasic monohydrate container, and two dibasic dihydrate containers (refer to Figure 2). Since the number of containers used for the weight was reduced by 50%, the associates will only use 25, 5, and 10 containers for the weighing (refer to Table 4).

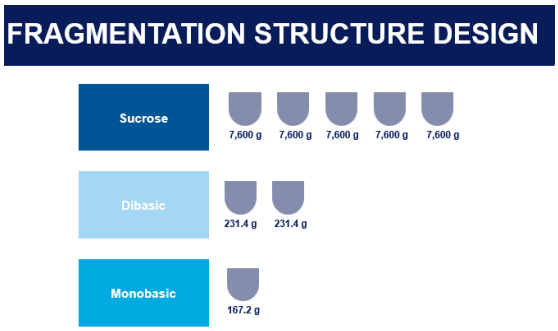

Figure 2
New Fragmentation Structure Design

Table 4
Fragmentation Maximum per excipient

Excipient	Fragmentation Maximum	Container weight per batch
Sucrose	25	Five containers of 7,600 g
Monobasic	5	One container of 167.2 g
Dibasic	10	Two containers of 231.4 g

Control Phase

This phase ensures that the solution is implemented correctly and documented. To ensure that the proposed changes were implemented, changes to operational documents (Work Instructions and Forms) were reviewed and updated. The main objective of standardizing the process is that every associate that performs the weighing uses the new fragmentation.

As part of the control phase, a new time study was performed (refer to Table 5) to confirm if the new fragmentation design reduced the time of the weighing. It was concluded that the time was reduced to 1.28 hrs. per batch, and the campaign was reduced to 6.40 hrs.

Table 5
Time Study Results (in minutes)

Excipient	Average Time	Normal Time	Standard Time
Sucrose	52.70	55.34	50.07
Monobasic	11.40	11.97	10.83
Dibasic	16.70	17.54	15.87

CONCLUSION

The project's main objectives were simplifying the weighing process to become more agile and increasing labor productivity and time effectiveness by distributing excipients grams in fewer containers. It can be concluded that all the goals set for this project were achieved. The weighing process time was reduced by 32.98% with the implementation of the new distribution. Also, since the new structure uses fewer containers, waste was reduced by 50%. Operational documents were reviewed and updated with further instructions for weighing, and data entries were decreased by 25%.

The main finding of this paper is that the change in the number of fragments has no impact on how the process is carried out except to update the number of fragmentations in the RMDU-related operational documents—also, a cost avoidance of approx. $13,000 will be obtained at the end of the year since the number of containers used was reduced. It can be concluded that any process can be improved; it only takes thinking outside the box and trying to do things differently. The weighing process for other products can be evaluated to conduct the same analysis. Also, processes can be standardized to reduce non-conformances and improve performance. It is essential to provide strategic training to manufacturing associates to guide them to follow the new improvements made to the operational process. Strategic training will improve the performance of the associates and will prepare them to execute at the best time possible. Implementing a mentoring system to improve performance and increase motivation is essential to increase productivity.

ACKNOWLEDGMENTS

This work was supported by the Large Molecule Business Unit of Janssen Pharmaceuticals at Gurabo, Puerto Rico. A special thanks to:

- Jose Diaz Garay (Associate MFG. Project Specialist) for supporting the project.
- Rolando Torres (Parenteral Sr. Manufacturing Supervisor) for providing support on the project and insights on the implementation plan.

REFERENCES

[1] Schniepp, S. (2021, October 2). *The Basics of Aseptic Processing.* Available: https://www.pharmatech.com/

[2] Cunha, J. (2021, October 13). *Remicade.* Available: https://www.rxlist.com/

[3] Mueller, M. (2020, July 15). *Process Simplification: Five Strategies to Improve Productivity.* Available: https://www.cafeprogessive.com/

[4] Lean Smarts. (2021, January 21). *Standard Work: The foundation for Kaizen.* Available: https://leansmarts.com/

[5] ASQ. (2023). *The define measure analyze improve control (DMAIC) Process.* Available: https://asq.org/

[6] Monday Blog. (2022, March 26). *Implementation Plan: how to carry out your project from A-Z.* Available: https://mondayblog.com

[7] Baumann, A. (2022, June 24). *Time Study 101: Overview, Steps, and Best Practices*. Available: https://blog.amper.xyz/