Formulation Process Optimization

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Abstract *— The field of biologics drugs development continues to grow and is becoming increasingly competitive. The manufacturing of biological medicines is a complex process that consumes a large amount of resources and time resulting in higher manufacturing costs in comparison of small molecules therapies. The lean manufacturing philosophy provides tools to identify areas of opportunity to optimize these processes by eliminating waste as activities that does not add value to the product. Buffer formulation is an inherent step in the biological product formulation process. Using the Value Stream Map tool in our buffer formulation process helped to find areas of opportunity that will allow recommendations to optimize the formulation process. In this way, it is possible to reduce manufacturing costs, increase capacity and have a better allocation of resources.*

Key Terms *— Biologic Drugs, Buffer, Formulation, Lean Manufacturing, Value Stream Map.*

BIOLOGICS DRUGS INDUSTRY

The biotechnology market in therapeutic medicine is one of the fastest growing markets with the development of promising products for conditions ranging from cancer, diabetes, heart disease, autoimmune, and even vaccine development [1]. Unlike traditional chemical molecules, these products are derived from living cells modified with biotechnology and genetic engineering techniques which require highly skilled technologically advanced capabilities [1]. The trend towards research and development of these drugs is due to their higher effectiveness in treatment, demonstrating relatively minor side effects compared to traditional small molecule products.

By 2022 the biotech market reached a market share of US$ 393.53bn, (see Figure 1) [2], and it is expected to hit over US$ 719.84 bn by 2030 [2]. Manufacturing is one of the most essential steps in the biologics production process, but due to its structural complexity, these processes are more complicated and expensive than small-molecule chemical drugs [1]. In a study published by Jamma Network in 2020 [3], the estimated cost of research and development of FDA-approved biologics between 2009 and 2018 is between $188.1m and $792.5m from research to approval. On the other hand, Forbes magazine published an article in 2019 [4] in which it mentions that the cost of producing a biological drug is estimated to be between $95 and $225 per gram. This cost is higher for new companies that do not have the capability to produce multiple drugs. In comparison, the cost of producing a gram of simvastatin, a commonly used small molecule drug used to lower cholesterol, is only 58 cents.

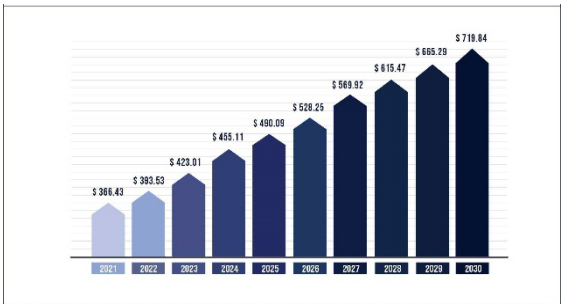

Figure 1
Biologics Drug Market Size from 2121 to 2030 (USD Billions)

Considering these points, it becomes evident that the industry must actively pursue continuous improvement with the implementation of tools that enable process optimization and maintain competitiveness in the market. These tools could not only improve the quality of the final product but also reduce total production costs and increase overall effectiveness, thus contributing to the success of the company.

VALUE AND LEAN PRINCIPLES

Lean manufacturing is a management philosophy that originated in the Toyota Production System (TPS) and was developed in 1950 by Taiichi Ohno and Eiji Toyoda to improve the efficiency of Toyota's manufacturing processes. The main goal of TPS was to eliminate waste and create value by focusing on value-added activities and reducing non-value-added activities. In the 1990s, the concept of lean thinking was popularized [5] by James Womack and Daniel Jones in their book "The Machine That Changed the World". The book highlighted the success of TPS and its applicability to other industries. Was about a time when Lean techniques became increasingly popular among companies seeking to improve their processes and reduce waste. The concept of lean manufacturing has been adapted to other sectors like healthcare, government, and the services industry.

Value and Waste

As mentioned before, Lean focuses on creating value by reducing waste. The definition of Value in Lean may be different from the traditional concept of value. By the Lean principles, the value of a product or service is determined solely by the end consumer [6], and it holds significance only when measured in relation to a particular item that satisfies the customer's requirements, both in terms of quality and cost, at a specific point in time. From the customer's perspective, producers exist to create value.

Another important concept in Lean is Waste. In the context of lean manufacturing, waste refers to any activity or process that does not add value to the end product or service from the customer's perspective [7].

There are several 7 types of waste identified in Lean:

- Overproduction: Producing more than is needed by the customer or producing too early, resulting in excess inventory.
- Waiting: Waiting for materials, equipment, or information can lead to delays and decreased productivity.
- Transportation: Unnecessary movement of materials or products, which adds to costs and can cause damage.
- Processing: Excess processing or processing steps that are not necessary or do not add value.
- Motion: Unnecessary or excessive movement of people or equipment, which can lead to fatigue and inefficiency.
- Inventory: Holding excessive inventory, which ties up resources and can result in waste due to obsolescence or damage.
- Defects: Production of defective products, which leads to rework, scrap, and additional costs.

By identifying and eliminating these types of waste, lean principles aim to improve quality, efficiency, reduce costs, and enhance customer satisfaction.

Value Stream Map

A value stream map (VSM) is a tool used in lean manufacturing to visually represent the sequence of steps and activities required to convert raw materials into a final product that meets customer requirements. It helps to identify waste by classifying activities in a process. In a value stream map activities can be classified into three categories [8]: Value-added activities, non-value-added activities, and required non-value-added activities. Value-added activities are activities that are essential to make a product a complete product. Required non-value-added activities are activities that do not add value but are essential for completing business processes; often imposed by government regulations or compliance procedures. Non-value-added activities are activities that do not add value and are waste. Removal of these activities does not affect end-product performance. Non-value-added activities are intrinsically related

to the seven types of waste discussed before and Lean aims to remove that waste.

FORMULATION PROCESS OPTIMIZATION

Drug Product facility manufactures biotechnological parenteral drugs commercialized to treat a wide range of conditions from autoimmune to cardiovascular. After achieving the Lean transformation Flow phase in 2017, the continuous improvement approach is embedded in the company culture and the internal business goals.

The formulation batches are required by the production schedule triggered by the Production, Planning & Inventory Control Department. The formulation of these products is classified into four platforms. 50% of the products manufactured in the facility are manufactured under Platform 1 and Platform 2. These two platforms are required to use a buffer solution which is required to be formulated prior Formulation batch occurs.

Formulation Process Overview

To optimize the formulation process, a High-level process map was defined to have a process overview. See Figure 2.

The first stage of the product formulation consists of a buffer solution formulated in a buffer suite. After formulating, the required buffer samples are collected and analyzed. After the buffer is released, it is transferred to a formulation suite. In the formulation suite, the transferred buffer is filtered and tested for endotoxins. Later, in the formulation step, the buffer solution is mixed with an active drug substance, and other excipients are added. Collection of in-process samples is required after formulation ends. Formulated product is transferred and filtered into a holding vessel until is required to be filled into vials or syringes.

Data obtained from previous standard work models establishes that the required time for products formulated under Platform 1 varies from 14.61 to 14.83 hrs. In contrast, products required to be formulated under Platform 2 require from 19.38 hours up to 23 hours to be completed, depending on each product.

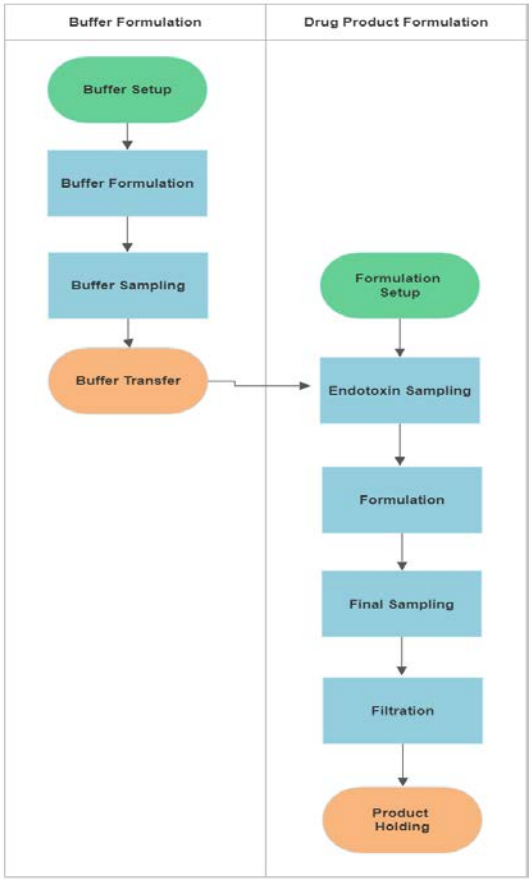

Figure 2
Drug Product Formulation High Level Process Map

Value Stream Map

Considering that the Buffer process is inherent in the drug product formulation process; the approach focused on measuring the buffer process and any improvement should be attributed to the formulation process overall.

A value stream map (VSM) was used to visualize the buffer formulation process and to measure the time elapsed in each process. Formulation Suite was established as our customer and dispensing area is identified as the supplier of raw materials. Data analyzed was obtained from the company database of the Electronic Batch record and the Process Control System. 32 formulation batches of Product A manufactured during the year 2022 were analyzed and the average of each step was used to establish the cycle time in

the VSM. Buffer formulation processes are mainly controlled by an automated system, it requires minimum intervention. Based on that, was easy to identify non-value-added activities like gowning, transport, and walking short distances. These non-value-added activities were subtracted from the cycle time. Figure 3 shows the Value Stream Map for the Buffer Formulation process. As shown in Figure 3 the Total Lead Time for the buffer formulation process is 350 mins/5.83 hrs. with only 99 mins (1.65 hrs.) of value-added activities.

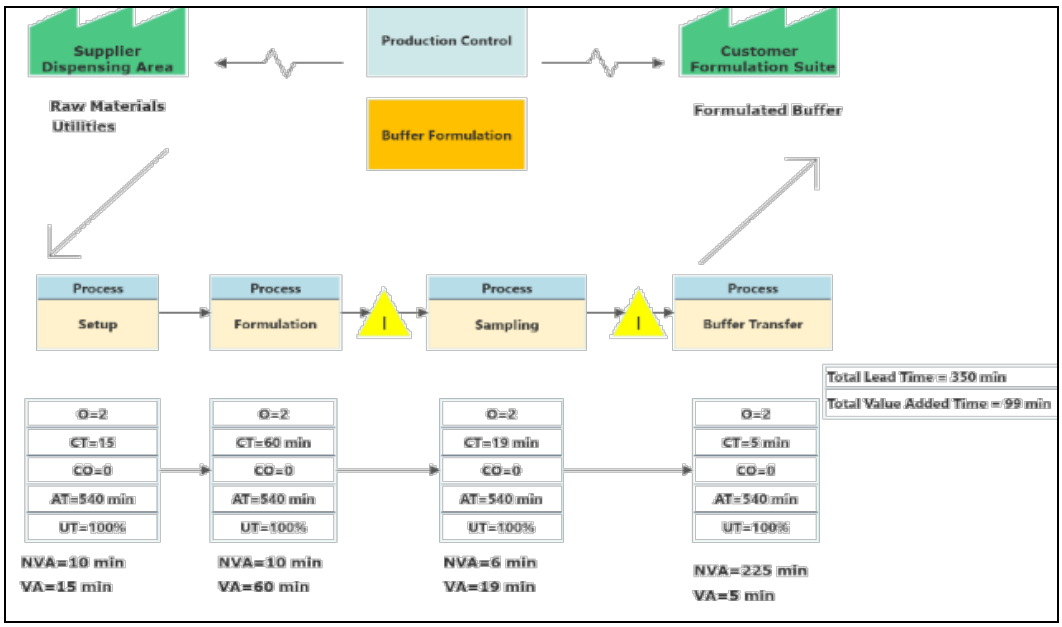

Figure 3
Buffer Formulation Process Value Stream Map

Results of VSM

VSM Results show that 71.71% of the time in the Buffer formulation process is categorized as waste. See Figure 4. Returning to the VSM, is easy to identify that the step with the higher NVA activity time is the Buffer transfer process.

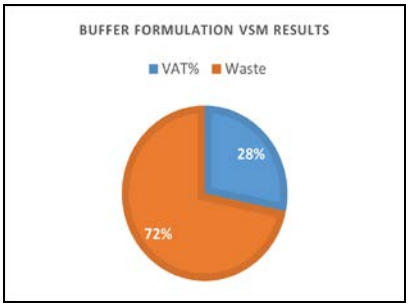

Figure 4
Buffer Formulation Process VSM Results Chart

Buffer transfer is the last step in the buffer formulation process. Standard operating procedures (SOP's) indicate that to complete the buffer transfer to the formulation suite; is required that the results from the previous sampling are approved. According to Lean principles, 225 minutes were identified as waste and classified as "waiting".

Current Formulation Strategy

With the current formulation strategy for Platform 1 and Platform 2, the Drug product formulation usually Is scheduled to start 2 hours after buffer formulation starts. Previous Standard work models for Product A establish that the setup time for drug product formulation is 100 minutes. Since drug product formulation cannot continue until the buffer is transferred, it results in an idle time limitation of 130 minutes.

For example, the total formulation time for Product A is 890 minutes or 14.83 hrs. from buffer setup to product holding. Figure 5 shows steps and elapsed time with the current formulation strategy.

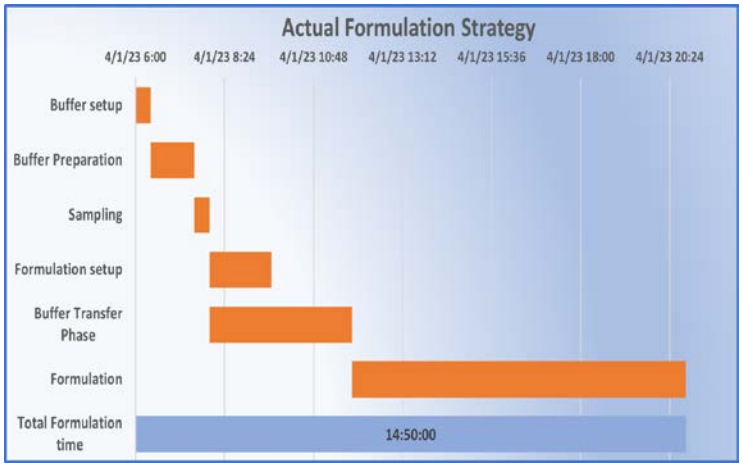

Figure 5

Current Formulation Strategy for Product A

Proposed Formulation Strategy

A new Formulation strategy is being proposed to optimize the formulation process time. By starting the formulation setup simultaneously with the buffer setup and transferring the buffer to the formulation suite after sample taking, the waste of waiting will be eliminated and significantly reduce the formulation time by 220 minutes or 3.66 hours. This means more efficient use of resources, increased productivity, and greater profitability after increasing the capacity to formulate more products. For example, for 2020, the formulation forecast included 199 formulation batches From Platform 1 and 139 from Platform 2, totaling 338 formulation batches. By implementing this strategy for the year, the plant would have saved 1,237 hours and maximized the capacity to formulate up to 63 batches from Platform 2.

Figure 6

Proposed Formulation Strategy

Cost Reduction

To evaluate the impact and cost savings; the attributable labor cost rate was retrieved from the ERP system. The actual rate of direct labor to formulate a Platform 1 batch is $188.76/hr. and $280.25/hr. to formulate a Platform 2 batch. With the current formulation strategy, the direct labor cost per formulated Platform 1 batch is between $2,757.78 to $2,799.3. After the new strategy implementation, the direct labor cost to formulate the Platform 1 batch will be between $2,066.92 and $2,108.45, which results in a saving of $690.86 per Platform 1 batch. For Platform 2 products, the estimated direct labor cost ranges from $5,431.25 to

$6,445.75 under the actual strategy, and with the proposed strategy the direct labor costs to formulate a Platform 2 product would be between $4,405.53 to $5,420.04 which means a saving of 1,025.72 per Platform 2 batch. The previous forecast required 199 batches from Platform 1 and 139 from Platform 2. The estimated savings in a year to formulate these batches could be estimated at $280,059.22.

Change Implementation

To Seek a change to the formulation process is required to implement it by a change control. Change control is defined as a formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment, and processes [9]. The evaluation team must involve support from Manufacturing, Automation, IS, Quality, Engineering, and Process Development. The change includes modification of SOPs, PCS recipe, and MES/EBR designs.

CONCLUSION

While the market share and the demand for biological products continue increasing, it is necessary to identify areas of opportunity that allow us to optimize manufacturing processes and increase capacity. Waiting is the easiest identifiable waste in Lean. The application of the VSM in the buffer formulation process helps us to easily identify the waste as the idle time during the buffer transfer phase. With the implementation of the proposed strategy, the formulation process time will improve by 25.28% and save approximately $280,059.22 in direct labor costs. This strategy is simple but effective. With the reduction in the formulation time, there is flexibility and agility to adjust the manufacturing schedule to meet market demand and the capacity to adopt the new products currently in development.

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