

# *Process Optimization by the Application of Lean Manufacturing Principles*

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**Abstract** — Commercial demand at a pharmaceutical facility in Juncos has been constantly increasing since 2016. Focused on process improvement strategies, our formulation capabilities were increased to support Drug Product requirements. These efforts resulted in a more agile and efficient manufacturing process by reducing 31% in lot lead time, 36% in batch record review process and absorbed an increase in lots by 9% (equivalent to 588 hours), thus increasing capacity from 2 to 4.07 lots per day without increasing headcount.

**Key Terms** — *Formulation, Lead times, Platforms processes, Process optimization.*

## **INTRODUCTION**

Nowadays, the pharmaceutical industry is in constant search for process improvements by avoiding the wastes of production outages (availability), ineffective product transitions (flexibility), and poor product quality (capability).

Process improvement efforts are started for many reasons. Traditionally, the primary goal has been to improve efficiency. Improved efficiency, or productivity, allows an organization to produce the same products with reduced effort. The pharmaceutical industry needs to be able to reduce the cycle times by improving the process and eliminating associated wastes. An ideal lean production, a plant can make any product at any time in any quantity [1].

Process improvement efforts; typically require new processes and procedures development, revision or optimization, training, and deployment activities.

## **Overview of the Pharmaceutical Industry**

The global pharmaceutical market is over \$700 Billion [2]. Three major market segments dominate the global industry: North America is the largest and comprises 53 percent, Europe is second with 26 percent, and Japan is third at 10 percent of 2007 sales [3]. Although these combined markets account for a large percentage of global sales, the remaining emerging market segments - other Asian countries, Africa, Australia, and Latin America - are growing rapidly.

Most of the industry's revenue is based on mega sales of blockbuster products, those that generate at least \$1 billion in sales. In 2006, the top 100 blockbuster drugs accounted for 36% of the total world pharmaceutical market [4]. However, many of the current blockbusters will be facing patent protection in the next few years, giving rise to the unbranded generics market, which has more than doubled in size since 2001 [5]. As early as 4 years after brand launch, a generic company may file with the FDA to challenge patents associated with the brand medicine, often allowing generic market entry before the patent expiration date [6].

## **The U.S. Pharmaceutical Industry**

The U.S. pharmaceutical industry (tiers 1 and 2) is comprised of approximately 100 companies. The U.S. not only has the largest pharmaceutical market in the world but also the only one without government controls. That characteristic has major consequences on drug pricing, innovation, and Research and Development (R&D) investment.

Strictly speaking, the term "pharmaceuticals" refers to medicines composed of small, synthetically produced molecules, which are sold by large, fully integrated drug manufacturers.

Most biotechs are small, research-oriented companies dedicated to applying genetics to curing a multitude of serious diseases, ranging from Alzheimer's to Multiple Sclerosis. A handful of companies such as Amgen and Genentech have broken through the rest of the pack to become "fully integrated" like Big Pharma. Biotech products are proteins, which need to be injected since they are very large molecules compared to the synthetic molecules Big Pharma sells. The largest biotechs are pharmaceutical companies in the way they function and are sometimes called "Big Biotech."

Companies are using acquisitions and alliances to round out their product pipelines and meet investor expectations. Big drug manufacturers can now claim to research, manufacture, and sell both synthetics and biologics. The biotech firms tend to be organized around smaller market products as their products are targeted to small patient populations with rare genetic diseases.

### **Overview of Operational Excellence**

Operational Excellence is the routine delivery of exceptional performance through a systematic approach to continuous process improvement. An operationally excellent organization leads its competitors by providing the lowest cost, highest quality product to its customers. It does this by performing the right tasks, at the right time, in the most efficient manner. Those firms that can achieve operational excellence realize increased customer satisfaction through shorter lead times and increased quality while decreasing operating costs and increasing overall profitability. Operating in a state of excellence creates a positive reinforcing loop in which value is added to the customer, increasing overall demand, resulting in firm profitability, which allows the firm to reinvest into new product development to provide new medicines to patients. Producing these new medicines in a state of excellence continues the cycle.

### **Lean as an Operational Excellence Methodology**

The principles of lean have become synonymous with operational excellence. Many of

the top-performing manufacturing and operations companies today have fully adopted this operating philosophy. Although there are other improvement methodologies widely used, like six-sigma and Total Quality Management (TQM). While there are many similarities between lean, six-sigma, and TQM, only lean looks at the entire enterprise and all its processes. Lean does not view quality as the sole factor in determining customer satisfaction as in six-sigma and TQM. Lean tries to optimize quality, cost, and speed simultaneously for the customer. Another key difference in these improvement methodologies is that while six-sigma and TQM try to maximize value as viewed by the customer, lean attempts to optimize value as viewed by all stakeholders.

### **Lean approach in Pharmaceutical Environment**

In a pharmaceutical environment, the lean concept represents a set of management practices that are set in place to improve efficiency and effectiveness by eliminating waste. The core principle is to reduce non-value-added activities. The non-value added, or wastes are defined as the performance of unnecessary work because of errors, poor organization, or communication. Eight (8) wastes identified as part of the Lean methodology can be established using the acronym DOWNTIME [7].

- **Defect:** refer to a product deviating from the standards of its design or the customer's expectation.
- **Overproduction:** can cause all other types of wastes and results in excess inventory.
- **Waiting:** refers to wasted time because of slowed or halted production in one step of the production chain while a previous step is completed.
- **Non-utilized talent:** non-utilized talent is exactly as it sounds; not effectively, or at all, utilizing the valuable resource that is your employees. This creates waste by leaving value on the table that your employees could bring through skills or talents that haven't been recognized.

- **Transportation:** transport itself adds no value to the product, so minimizing these costs is essential. Transport can also cause the waste of waiting, as one part of the production chain must wait for material to arrive.
- **Inventory:** refers to the waste produced by unprocessed inventory.
- **Motion:** Wasteful motion is all the motion, whether by a person or a machine, which could be minimized. If excess motion is used to add value that could have been added by less, than that margin of motion is wasted.
- **Extra-processing:** refers to any component of the process of manufacture that is unnecessary.

## **RESEARCH DESCRIPTION**

The research will be carried out concerning the best batch record documentation approach considering the constant changes in the pharmaceutical industry. A simple methodology will provide the flexibility needed in the manufacturing environment, improve the processing times, and lower the costs that in present days represent an advantage in the competitive business.

### **Objective**

Operational Excellence (OPEX) is essential to the future commercial success of the pharmaceutical industry. In an industry that is facing bio-generics, pricing scrutiny, and decreasing new drug productivity with increasing R&D expenditure, OPEX is not just a competitive advantage; it is a competitive necessity. The goal of this project is to examine the current competitive challenges facing the pharmaceutical industry formulation process and propose a new systematic approach that will help achieve excellence within the pharmaceutical operation that is essential to future success.

The objective of the project will seek to implement a simple, robust, and compliant batch record documentation system, establish the formulation platforms and improve the cycle time

of the formulation process, by providing a new approach within the established process and procedures as part of this project.

Defect and Extra-processing wastes will be the focus of this project. Defective products must be replaced; they require paperwork and human labor to process it; the resources put into the defective product are wasted because the product is not used. Moreover, a defective product implies waste at other levels that may have led to the defect, to begin with; making a more efficient production system reduces defects and increases the resources needed to address them in the first place. As mention before, Extra-processing implies to put more effort and adding more value than the customer requires.

### **Operational Excellence Contributions**

Historically the pharmaceutical industry has been highly profitable. However, the increasing regulatory requirements, bargaining power of buyers, and drug failures together with the threat of biosimilar and decreasing R&D productivity are creating challenges for research-driven pharmaceutical companies. With future revenue growth, uncertainty, pharmaceutical companies must focus on cost reduction to sustain the profit margins needed to support manufacturing production.

## **METHODOLOGY**

A six-step process incorporating the key principles behind the highly successfully six-sigma DMAIC (Define, Measure, Analyze, Improve, Control) methodology and those of lean manufacturing will be used as guideline to optimize the manufacturing process (see Figure 1)[8].

The lean methodology first developed by Toyota is recommended to achieve operational success. Substantial improvement opportunities exist within the current pharmaceutical manufacturing process that companies must build operational efficiencies into manufacturing process designs. This stepwise process is a defined

approach to the execution of the short-term cycle of the transition that will help develop an optimized process.



**Figure 1**  
DMAIC Methodology

### Define Phase

Lean improvement activities began with the opportunities identified through the process overview discussion. The first step in a lean transformation is "learning to see". The main benefits of this activity were:

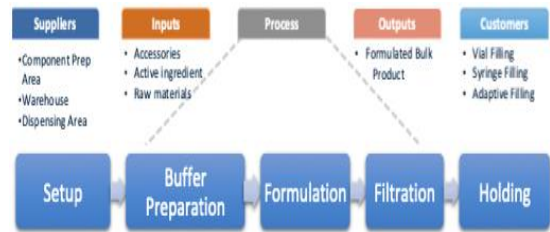
- Allowed process visualization.
- Helps identify the process steps with the greatest significance.

A project charter was developed to define the focus, scope, and direction of the improvement team. Voice of the customer executed help to understand customers' needs and expectations. A general overview was developed based on current process execution to identify areas of opportunities.

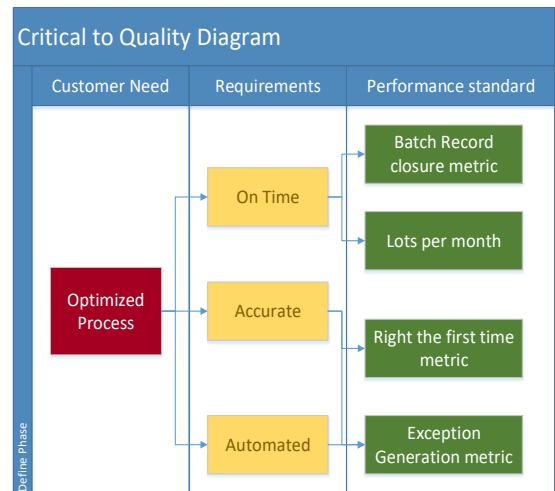
Another tool used in the Define phase of this project was the SIPOC diagram. This was developed to define the boundaries of the project scope. SIPOC diagram is an effective tool to study the process, which can identify key activities as outputs and inputs throughout the process. SIPOC diagram generated is shown in Figure 2. This will help transition into a key activity, being that it is a tool to identify preliminary requirements of the customers for those outputs.

Key functional areas were included as part of the discussion to identify areas of opportunities.

The discussion covered specific topics related to the documentation process and process execution. This activity was key to identify the CTQ (Critical to Quality). The Critical to Quality diagram (Figure 3) guide part of the research about the critical quality aspects that relate to the demands and necessities of the customer.



**Figure 2**  
SIPOC Diagram



**Figure 3**  
Critical to Quality Diagram

For this project, we will focus on the documentation aspect and requirements identified during the Define phase.

### Measure Phase

The measurement takes place throughout the life of the project, but a key question to answer in the Measure Phase centers on how the process currently performs. Figure 4 illustrates the measured data. A total of 24 batch records and 18 procedures were identified as part of the project scope.



**Table 2**  
**Formulation Process Stages**

Stage	Formulation process									
	A	B	C	D	E	F	G	H	I	J
Setup	x	x	x	x	x	x	x	x	x	x
Buff. Transfer	x	x								x
Buff. add	x	x								x
Ing. add.	x	x								x
Act Ing. add.	x	x	x	x	x	x	x	x		x
Ing. add.			x							
QS	x	x								x
Filtration	x	x	x	x	x	x	x	x	x	x
Clearance	x	x	x	x	x	x	x	x	x	x

**Table 3**  
**Formulation Process Stages**

Stage	Formulation process				
	K	L	M	N	O
Setup	x	x	x	x	x
Buff. transfer	x	x	x		x
Buff. add	x		x		x
Ing. add.					
Act Ing. add.	x	x	x	x	x
Ing. add.	x	x	x	x	
QS	x	x	x	x	x
Filtration	x	x	x	x	x
Clearance	x	x	x	x	x

Process execution commonalities were identified in the buffer preparation and formulation processes and procedures. Although they share process stages, each of the products remained separate in their corresponding procedure. Evaluated procedures provide the instruction to complete the buffer preparation and formulation process. However, there are no standardized instructions when comparing similar processes. The fact that each process is independent and has its own set of instructions does not allow the functional area to be as effective as it should. Lead-time is impacted based on the process being performed and instructions provided. In terms of documentation system, each process execution is documented in individual designs. The documentation system follows the same strategy as the standard operating procedures.

### Improve Phase

As part of the Improve phase in the DMAIC methodology, all proposed changes were implemented. Changes includes, updates in

Standard Operating Procedures and Batch Record designs.

### Standard Operating Procedures

Based on the finding of the Analyze phase, the future stage was developed to improve overall process lead times. Commonalities identified during the analyzed phase, allowed to develop a platform strategy for buffer and formulation area. Buffer preparation instructions were consolidated into one (1) standard operation procedure with one (1) supporting document. All common steps were established in the procedure while the specific requirements were transferred into a supporting document. For the Formulation area, the platform approach allowed to group the different formulation processes into one of the three established platforms.

- **Platform Type A:** Laboratory results trigger an adjustment to product based on active ingredient concentration using a buffer or intermediate solution.
- **Platform Type B:** No buffer or intermediate solution is needed. Only the active ingredient is added into the mixing tank.
- **Platform Type C:** A target weight or volume is reached to complete the process.

All common process instructions were consolidated into one (1) standard operating procedure and three (3) supporting documents; one for each platform. The supporting documents provided specific instructions to complete the formulation process.

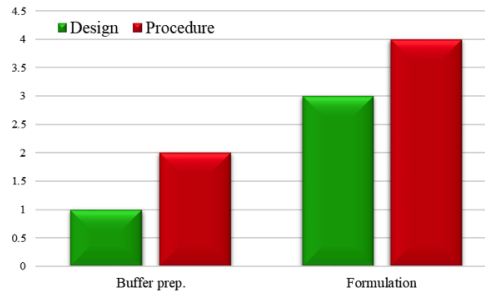
The implementation of the platform allows the standardization of all the different processes, providing the same instructions and requirements for each of the platforms. Standard Work was created to aid the standardization of all formulation related activities. Figure 8 shows the proposed strategy for the documentation system and procedures.

### Batch Record Designs

The platform approach was also applied to the documentation system. Four new designs were proposed for the buffer preparation (1) and formulation area (3). To increase the benefit of this, optimize designs, Manufacturing Execution System



(MES) capabilities will be activated to allow data transfer between designs. Specific product requirements such as Tank usage, Excipient requirement, and critical process parameter ranges were transferred to the parameter value list in which information is retrieved by each of the SKU during the formulation process. Non-value-added activities were removed to promote a lean documentation process while remaining in compliance with the regulatory and operation standard requirements for the pharmaceutical industry.



**Figure 8**  
**Proposed Strategy**

As discussed in the measure phase, the exception generated increase de lead time since additional work is needed. This new functionality will minimize the manual entry; therefore, the possibility of an incorrect value being entered in the batch records.

In addition to the MES capabilities that were activated, real-time communication with the process control systems integration was proposed for the batch records. System integration will allow a data transfer from the control system to the documentation system. Alarms and recipe changes generated during buffer preparation and formulation process are automatically transferred without the necessity of additional operator actions, improving the resource availability during activity execution.

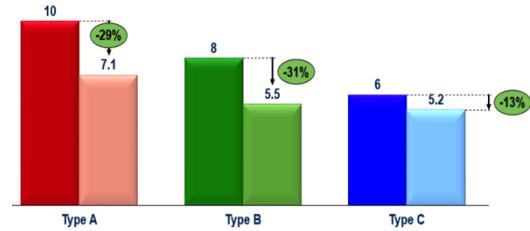
**Control Phase**

Control phase allows monitoring all implemented changes, and completes the DMAIC methodology.

**Formulation Lead Time**

After the implementation of the proposed strategy, the formulation lead time (Figure 9) were

reassessed to determine strategy results. Improvements resulted in a reduction in formulation time. Manufacturing capacity increased from 2 to 4 lots per day, without increasing headcount.



**Figure 9**  
**Improved Formulation Lead Time**

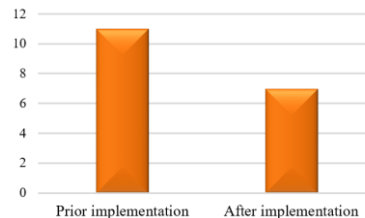
**Right the First Time**

A 50% reduction in Error during execution, a 71% reduction in Exception generation, a 48% reduction was achieved for the deviations related to the method and 12,380 manual entries were eliminated improving the Right the First-Time metric.

**Resource allocation**

In addition to a reduction in formulation lead-time, the following benefits were achieved. An 83% in SOP reduction, a 79% reduction in MES designs a 44% reduction in design validation activities, a 77% reduction in batch record readiness time, and a 50% reduction in document readiness time improving resource allocation for the Manufacturing Support functional area. This represents a reduction of 2,832 working hours per year.

By improving the time spent in formulation activities, allowed the reallocation of the manufacturing resources to absorb additional tasks required to support the manufacturing operations.



**Figure 10**  
**Batch Record Review Lead Time**

As described in Figure 10, a 4-day reduction in batch record review and approval metric was observed.

## CONCLUSION

To secure a competitive edge in the pharmaceutical industry as a biotechnology company, the organization seeks out ways to increase efficiency and guarantee the successful execution of critical business processes. In today's global business environment, the importance of first-to-market, cost-competitiveness, and quality are key factors in determining an organization's success. The current and future commercial demand can be allocated at the commercial facility because of the optimization of the formulation process documents and batch record designs. The new and optimized process will serve as a standard for future product or process introduction. When operating in a highly competitive market, it is more difficult to implement improvements because of commercial requirements. The lean methodology allowed to increase manufacturing capacities, reduce operational costs, and increased the robustness of the documentation systems without impacting the commercial production schedule.

In today's global business environment, the importance of first-to-market, cost-competitiveness, and quality are key factors in determining an organization's success. The first-to-market strategy demands a constant process monitoring to identify areas of opportunities. With this factor as the main goal of this project, the Formulation process lead-time reduction was achieved, fulfilling the gap to remain as one of the top companies in the pharmaceutical industry and leader in the application of molecular genetics.

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