Process Improvement and Inventory Management using Value Stream Mapping in a Biopharmaceutical Environment

by

Zachary Wolf

B.S. Civil Engineering, United States Coast Guard Academy, 2009

Submitted to the Department of Mechanical Engineering and the MIT Sloan School of Management in Partial Fulfillment of the Requirements for the Degrees of

Master of Science in Mechanical Engineering
and
Master of Business Administration

In conjunction with the Leaders for Global Operations Program at the Massachusetts Institute of Technology

June 2013

Signature of Author _____
Department of Mechanical Engineering, MIT Sloan School of Management
May 10, 2013

Certified by _____
Stan Gershwin, Thesis Supervisor
Senior Research Scientist, Department of Mechanical Engineering

Certified by _____
Don Rosenfield, Thesis Supervisor
Senior Lecturer, MIT Sloan School of Management

Accepted by _____
Maura Herson, Director of MIT Sloan MBA Program
MIT Sloan School of Management

Accepted by _____
David Hardt, Chairman, Committee on Graduate Students
Department of Mechanical Engineering

PROCESS IMPROVEMENT AND INVENTORY MANAGEMENT USING VALUE STREAM MAPPING IN A BIOPHARMACEUTICAL ENVIRONMENT

by

Zachary Wolf

Submitted to the MIT Sloan School of Management and the Engineering Systems Division on May 10, 2013 in Partial Fulfillment of the Requirements for the Degrees of Master of Business Administration and Master of Science in Mechanical Engineering

Abstract

This thesis describes the formulation of short-term and mid-term operational excellence strategies through the use of value stream mapping. It is shown that many interconnected issues form a backdrop for seemingly independent "symptomatic issues" or issues that can be seen readily on the surface because of their significant financial or organizational impacts. These underlying issues indicate organizational improvement projects are necessary in the short term to create an environment conducive to sustaining results stemming from projects addressing the surface issues. One example of a surface issue is that of scheduling where the problem can be readily seen with blockages, starvation, and long cycle times, but must be solved with organizational and other fundamental improvements for improvements to be sustainable. Also presented is a case study showing a root cause and financial analysis relating to the capabilities of the aseptic filling process. The value stream mapping analysis led to recommendations of working on fundamental organizational, communication, and cultural issues to create a strong foundation for improvement projects on more visible projects.

Thesis Supervisor: Stan Gershwin, Thesis Supervisor
Title: Senior Research Scientist, Department of Mechanical Engineering

Thesis Supervisor: Don Rosenfield, Thesis Supervisor
Title: Senior Lecturer, MIT Sloan School of Management

This page intentionally left blank.

Acknowledgments

I would like to express sincere gratitude to Novartis Vaccines and Diagnostics for sponsoring this internship, especially to all the fantastic people of the IQP team (Dave, Karen, Mark, Ian and Shana) and to my supervisor, Antonello. I also wish to acknowledge the Leaders for Global Operations Program for its support of this work. In particular, I am very thankful to my advisors, Don Rosenfield and Stan Gershwin for trekking all the way to Tuscany to support my project.

Grazie mille a tutti gli amici italiani. La vostra gentilezza e generositá non saranno dimenticate. Inoltre, grazie per avermi insegnato a giocare a calcio e per aver visto assieme i Campionati Europei di Calcio.

To Stefano, thanks for being a great friend. From basic questions about living in Italy to complex work related questions, you always had an answer and supported me the entire time I was in Italy. I am excited to someday soon see Napoli from your perspective!

To Carolina, thank you. And to the entire family (including Asia), thank you for making me feel as if I was a part of your family and for providing me a supporting relaxed environment that allowed me to be refreshed and ready for work every Monday. From Milano to Le Cardete to the Maldives, it was an honor to get to know you all.

To my fellow European LGO's, it was fantastic to bond with you over Eurogiving. Thank you for being great sounding boards and for providing sound advice on both the project and thesis. And, to Liz and unborn Henry, I appreciate you understanding Peter and my lack of directional skills in both the Cinque Terre and Roma.

To Mom, Dad, and Kayley, thank you for supporting my adventures in Italy and for driving me to achieve my goals. I love you!

This page intentionally left blank.

Table of Contents

Table of Figures

Thesis Introduction

1.1 Introduction to Value Stream Mapping

This section provides an overview of the methods used to analyze the aseptic operations at a vaccines manufacturing plant.

1.1.1 Overview and Benefits of Value Stream Mapping in the Pharmaceutical Environment

A "value stream [is] the set of all specific actions required to bring a specific product or service through the critical management tasks" [1]. In turn, a thorough understanding of the value stream is imperative to effective operations, especially complex manufacturing such as those required found during aseptic operations in the biopharmaceutical space. Such manufacturing requires a precise understanding of how each step relates to another, the capabilities of each process step, and the gaps between the current state and an improved future state. In part because of these requirements, "value stream mapping is an effective and proven tool to assess existing business processes and to re-design them based on "Lean" concepts" [1].

1.1.2 Value Steam Mapping Process Overview

Mapping the value streams of the aseptic segment required enough precision to have actionable findings, yet be broad enough that the value stream mapping process could be repeatable and continue to be updated without inordinate effort. To map the aseptic value streams, the segment was divided by families of products that shared similar characteristics. From there, metrics were standardized globally and data was collected for each line and family, respectively, to allow for the new metrics to be measured. The current state value stream maps were then created allowing for more in depth analysis. After determining significant and workable projects, a desired future

state could be envisioned. Finally, an improvement strategy for the short and mid-term projects was created to convey a clear vision of expected improvements.

1.2 Value Stream Mapping Drivers

In an ideal world, managers and operators would know all aspects of their process allowing them to make constant improvements to better the process. It would not be necessary to map out all knowledge because it is already known and being acted upon. However, in reality, the aseptic process inherent in all vaccine production is highly complex with numerous metrics and variables to keep organized. In order to prevent the overly prevalent the "gut-based" decision-making that comes when a clear understanding of the process is lacking, value stream maps are required. Therefore, since the aseptic process had never been mapped, there was a significant need.

1.2.1 Cost Drivers

Vaccine production is a commodity business, especially when contrasted with the closely related, highly profitable, pharmaceutical industry. Unlike the more profitable "reactive" drug industry, the preventative drug industry has historically low margins [2]. While new blockbuster drugs are changing the shape of the industry and promising increased profitability, Novartis's potential blockbuster (Bexsero) has yet to reach commercial operations [2]. Therefore, while the future looks bright, current profitability is very low. This is clearly evidenced by the most recent fiscal year, 2012, in which Novartis Vaccines posted a quarter billion dollar loss, 13.5% of sales. This is trending average for the division over the past 2 years as Vaccines lost 249 million dollars in 2011 [3].

Much of these losses are due to manufacturing losses and process failures as half of all batches started are written off [4]. Since the vaccines division is one of the newest acquisitions to join the company that has traditionally been able to turn a substantial profit based on research excellence as opposed to manufacturing and supply chain excellence, the vaccines and diagnostics division is in a unique place in the company in that operational excellence is key to the vaccine division's profitability [3]. As an early step on the operation excellence journey, it was recognized that in order to reduce losses, it was necessary to understand the specific sources of the losses and the causes of the losses.

1.2.2 Capacity Constraints

The overwhelming consensus amongst managers and operators in the aseptic area is that demand is outstripping capacity. While this perception of low capacity will be shown to have other causes, the ability to get all products through the vial and pre-filled syringe lines at the appropriate time remains a challenge. Some of the capacity issues are caused by an inadequate planning process that causes frequent, and disruptive, schedule changes. Despite this, the demand for aseptic services within the division is very high and looks to show significant growth with the introduction of Bexsero because of its expected high sales volume [3]. While these scheduling issues are very apparent on the surface with starvation, blockages, long queue times, and extending cycle and lead times being the symptoms, the scheduling issue needs to be addressed at its core with fundamental organizational and cultural changes.

1.2.3 Cultural Drivers

One of the most easily ignored, yet most important reasons for mapping the aseptic value stream is to change the cultural norm of the Novartis Vaccines Division. Before the start of the project, the culture was not one of relying on data. From the perspective of most managers on the shop

floor, data represented mistakes and faults that might warrant punishment, not opportunities for improvement and therefore accolades. The goal was, by mapping the processes, to show that all areas have opportunities for improvement and give a path for improvement that is based on fact, not gut or experience alone [5].

1.3 Problem Statement

The goal of this research is to create an implementable short to mid-term (3-5 year) strategic plan for operations improvement and write-off reduction through the use of the value stream mapping technique. Further, the project is designed to be the impetus for bringing about a full-fledged value stream mapping program throughout the business through a culture shift from gut-based decision making to a reliance on the data.

1.4 Thesis Structure

This thesis will begin with a review of the biopharmaceutical industry and will narrow scope to Novartis, the division in question (Vaccines and Diagnostics), the specific site (Rosia, Italy), and finally to the actual segment under consideration (aseptic). Following this overview, there is an overview of the existing literate on value stream mapping techniques.

After setting the stage, the next two chapters deal with the specific approach taken to achieve the final results. The methodology and results are discussed. This section explores the interconnected nature of the issues seen in the aseptic area the underlying problems that exist.

Next, is an example of further analysis that was conducted that will serve as a baseline to a future project to greatly reduce aseptic write-offs. This project is typical to those that should be continued to implement all aspects of the strategy formulated with this research.

Finally, the thesis concludes with the high level conclusions that can be drawn from the research and recommendations for moving forward. It also draws in current projects that are currently underway in Rosia in accordance with the strategic plan formulated in this thesis.

2 Biopharmaceutical Manufacturing Background

2.1 Novartis Group Background

Novartis is a very large pharmaceutical conglomerate reaching well over 1 billion patients on an annual basis [3]. Novartis is also well known for its rich pipeline with over 200 new products in clinical development [3]. The group has 6 major divisions: Pharmaceuticals, Vaccines and Diagnostics, Generics, Consumer Health, Eye Care, and Research and Development. Primary operations take place around the world while the company is headquartered in Basel, Switzerland [6] [7].

2.2 Novartis Vaccines Background

Novartis Vaccines believes that "the only thing better than finding a cure for a disease is preventing illness in the first place". Novartis Vaccines, now the fifth largest vaccine manufacturer overall and the second largest producer of the influenza vaccine, came into being following the Novartis acquisition of Chiron. The business is headquartered in Cambridge, Massachusetts; however, most production occurs at facilities in Italy (Siena and Rosia), Germany (Marburg), the United Kingdom (Liverpool), and elsewhere in the United States (Holly Springs and Emeryville) with new facilities in the emerging markets of India, China, and Brazil [7].

Novartis Vaccines employs 6122 employees in 30 countries and has annual revenue of 2.0 billion (3.4% of total group revenue) [8]. However, vaccines are viewed largely as a commodity and therefore have low margins. In fact, the business operated at a loss in 2012 [3].

2.3 Innovation, Quality, Productivity (IQP) at Novartis V&D

Novartis Vaccine's lean six sigma journey began in 2007 when the Innovation, Quality, and Productivity Group was formed. It initially was very small (with only one person) and has grown steadily in number and vision in the past five years. The training of personnel (both black and green belts) has been one of the cornerstones of the group since its inception. As can be seen in the below diagram, the IQP group now focus to forward looking Operational Excellence projects and improvements instead of retroactive/remediation type activities.

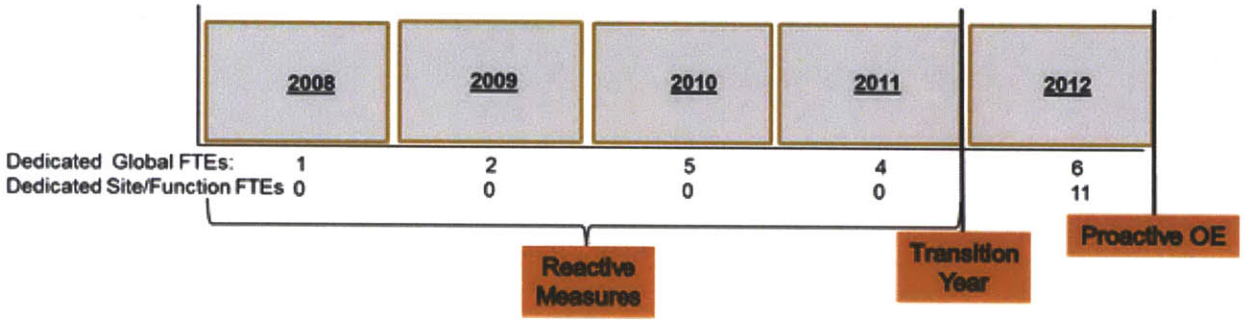


Figure 1: Novartis Vaccines Operational Excellence Journey [9]

In this diagram, FTE refers to "full time employees" and OE stands for "operational excellence". Imbedding the use of value stream mapping and focusing on the data have also been strong initiatives coming from the group with intensified focus since the close of 2011.

2.4 Overview of Aseptic Operations

Aseptic Operations are widely viewed as the most complex portion of the vaccine manufacturing process. The term aseptic operations refers to manufacturing within tight air quality and sterility specifications to ensure that product is not contaminated. While this significantly increases the

complexity and costs of manufacturing, it is important to ensure that the drug product is safe to be injected into patients. Specifications are set by the regulatory agencies of the product's destination country and are organizations such as the US Food and Drug Administration (FDA) and country specific ministries of health. Additionally, because Novartis is dedicated to improving the lives of patients around the world, Novartis Vaccines has implemented additional quality standards and controls in addition to the already strict government regulations that are applied to the release of all vaccines. This is to ensure that all products released to the customer are safe and effective and produce the best possible outcome for the patient. All aseptic processes are strictly scrutinized making thorough documentation and certification of all process steps critical.

2.5 Rosia Aseptic Operations

Rosia is the primary aseptic production site with most products passing through the facility. In fact, the facility is designated the "center of excellence" for aseptic operations in the Novartis network [10]. Rosia receives antigens, the active ingredient in most vaccines, from numerous sites throughout the network creating a complex inbound supply chain. After receipt, the final formulation occurs followed by the product being filled into prefilled syringes (PFS's) or vials as shown in Figure 2. The outbound supply chain is much simpler as the primary customer (packaging) is located on the same facility in a building that is physically connected.

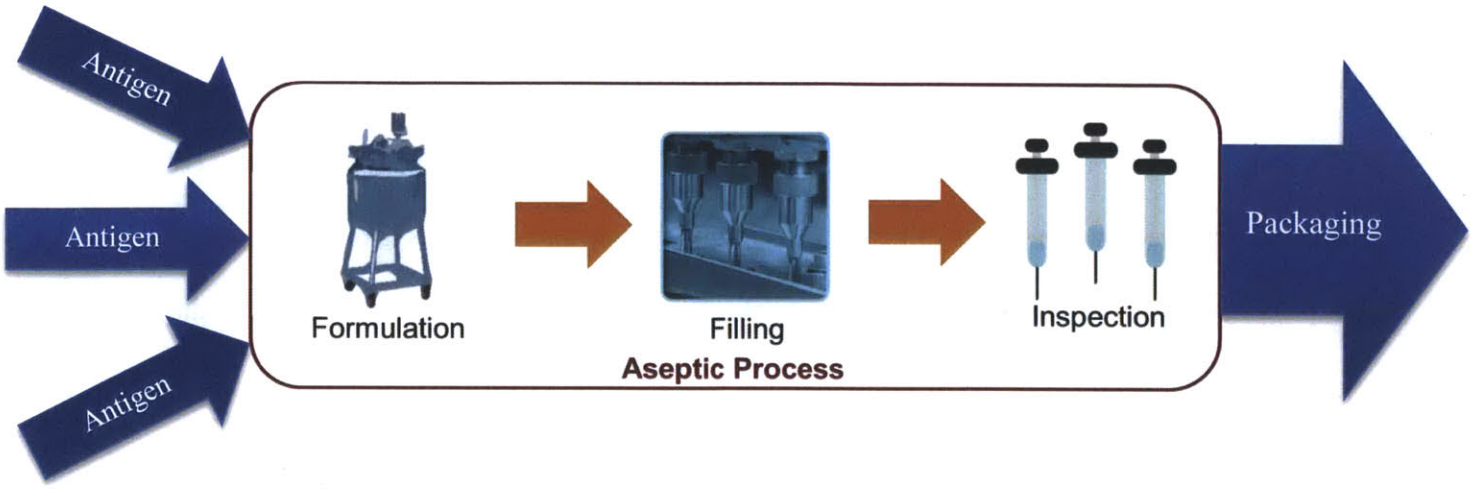


Figure 2. Significant Steps In The Aseptic Process Including Inputs and Outputs

Over 300 people work in the segment with many of the workers being on temporary contracts. These workers mainly support the three primary PFS lines and the Vial line. There are other smaller lines in the segment, but those are not the focus of the research.

2.6 Segmenting the Area for Value Stream Mapping

To obtain precise enough information to have actionable results from the value stream map, the products were divided into product families a can be seen in the following figure:

Product Family	Key Characteristics
Adjuvant	The adjuvant product family encompassed all non-flu products that had an additive to modify the effect of the vaccine's antigen. The most common adjuvant used in the vaccines produced by Novartis Vaccines is Aluminum Hydroxide, known more commonly as Alum. This accounted for nearly all products not related to Influenza besides Menveo.
Flu with MF59	This product family encompassed all influenza preventing products that contained the MF59 additive. MF59 is an adjuvant that is added to the flu vaccine to increase the antibody and T-cell response of the vaccine. In addition, the MF59 additive has been shown to increase the cross-reactivity of the vaccine to virus strains not specifically covered by the vaccine [11].
Flu without MF59	All influenza products without the MF59 additive are included in this product family.
Menveo	Menveo is a very complex meningococcal vaccine that protects against four of the five most common strains of Meningitis that occur in the United States. Because the vaccine protects against four unique strains, there are four distinct proteins (antigens) that must be blended into a single vaccine thereby increasing the manufacturing complexity [12].

3 Review of Existing Literature Relating to Value Stream Mapping

This section will describe the established thought on Value Steam Mapping. While the exact process for conducting a Value Stream Mapping exercise varies even between industry experts,

general themes have emerged and the multiple methods, including those laid out in Mike Rother and John Shook's *Learning to See,* and these have been synthesized below [13]:

1) *Determine Product Families*

   The Value Stream Mapping exercise is greatly simplified by focusing on creating proper families that share not only similar process steps, but also similar characteristics. Further, by selecting homogeneous families, the benefit is maximized as the results are usually more specific and therefore more implementable [14]. In the pharmaceutical environment, it was found that other factors such as product consistency, drug function, and season of production/campaign were very important to consider in the formulation of product families.

2) *Understand the Perceived Problem*

   It is important to understand the issues at hand from both the perspective of the process's customer as well as other stakeholders within the organization [14]. The first primary benefit from understanding the problem at multiple levels is that the value stream map should include the correct metrics to address all the issues. For example, the customer might not be concerned that the process has a large expected amount of waste built into the product, but other stakeholders such as engineering, operations, and finance may see this as an issue and an opportunity to improve yields and lower costs. Another significant benefit in interacting with many stakeholders when determining the process's issues pertains more closely to the practical matter of implementation. The creation of the Value Stream Map requires the support of numerous departments and functions. Through forming good working relationships with the personnel in these departments, it is more likely that they will be willing to dedicate resources and time to complete the

map. Further, by knowing all issues, the Value Stream Map is more likely to address the primary causes for concern and understand connections between issues and, at the conclusion of the process, solve these problems. In the end, solving problems about which the stakeholders have expressed concern will create buy-in for further projects and likely provide the best improvement for process efficiency, throughput, and productivity.

3) *Walk the Value Stream*

Gemba, the Japanese word for "actual place" is commonly used in the manufacturing setting to denote that one must "go and see" to fully understand the process. Going to the actual work site ensures that miscommunications on explanations do not occur, that those creating the Value Stream Map understand the work environment and culture, and so that people can see for themselves seemingly minor points that could be missed during an oral explanation of the Process [1].

4) *Collect Pertinent Data including Times and Key Metrics*

From precious conversations with stakeholders, key metrics will be able to be identified. Standardization of these metrics is important to ensure continued used and for benchmarking and to ensure that all in the company are speaking the same language with the same operationals definitions. After the metrics are identified, it is imperative to ensure all data is either being collected or that the gap is identified so future data can be obtained.

Data collection ideally will be based on physical observation whenever practical. In the biopharmaceutical vaccine industry, it is often not practical to observe a process step multiple times as each step can be many hours or days in duration. In this case, estimates of the data should be provided by historic records or by the operators themselves [1].

However, if using the estimates of the actual associates performing the action, it is important to understand the biases that may consciously or subconsciously affect their answers.

5) *Draw the Map*

The Value Stream Map should be drawn by hand. It is acceptable for later drafts for the map to be made electrically, but it is not mandatory. Common technique is for the value stream map to be drawn on large sheets of paper with adhesive notes to denote the data for the process steps. This is done such that the actual map is accessible, not just a document on lost in a computer system. The map should be created by all those who are involved in a process, not just those with computer access. Additionally, the map should be posted in a visible place such that it is frequently on the mind of those involved in making the process, from operators to managers.

6) *Identify Opportunities for Improvement/ Identify a Future State*

After completing the map, it becomes necessary to focus on the key drivers of success and to identify what will cause the greatest improvements. This could involve many steps including challenging each step to determine which steps create value (and eliminating steps that do not), attempting to achieve continuous flow wherever possible, and leveling the value stream [14]. It is also important to identify the underlying causes of problems and any interconnectivity that might exist between issues.

7) *Create Strategy for Improvement Implementation*

Because of scarcity (of resources, budget, and personnel), not all improvement ideas will be implemented. For this reason, it is critical to create a prioritization method that not only takes into account the effects of the improvement, but also the cost. When creating

this strategy to reach the future state, the value stream mapper must design a future state that can be achieved in a reasonable timeframe [1]. The appropriate time frame will differ based on a number of factors (including industry, cash on hand, and company culture), but one year is considered to be a reasonable timeframe [1]. In the pharmaceutical industry, timelines are somewhat longer because of regulatory hurdles and the campaign manufacturing nature of the business.

8) *Repeat Cycle on a Regular Basis*

Because the process will not be perfected after one Value Stream Mapping exercise, the process must be repeated for the best results. Further, besides alerting managers to potential improvements to their processes, value stream maps are valuable in that they provide managers and operators the ability have a deeper understanding of the current state of the process. Continuous mapping of value streams allows owners to know the process deficiencies at all times and demands thorough understanding of the process.

4 The Methodology for Value Stream Mapping the Aseptic Process

This section describes the approach used for mapping the Aseptic Process at Novartis Vaccine's Rosia Site.

4.1 Scope Definition

The original project scope was defined as being bounded by the four walls of the aseptic area, but was narrowed to only include major products and those with the potential for long term production. This meant that all products and processes within the aseptic area were within scope. However, once it was discovered that a specific high volume product was being discontinued in the next fiscal year, that product and its dedicated line were removed. Similarly,

low volume products on lines other than the four primary vial and pre-filled syringe lines were removed from scope.

The four wall approach includes scheduling and in-process inventory, but not the complete supply chain or warehouse. The following SIPOC demonstrates the scope and the process's customers and suppliers along with the overall scope. The name SIPOC is an acronym that comes from the chart's function of clearly defining a process's suppliers, inputs, process, outputs, and customers.

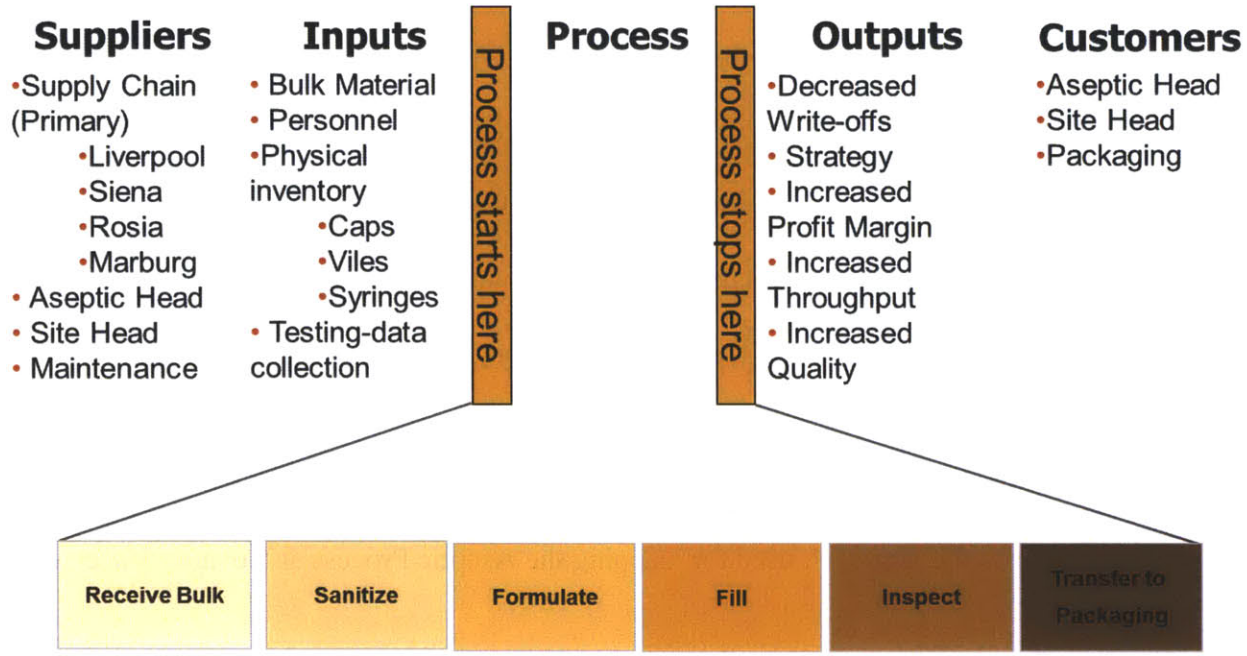


Figure 3: SIPOC chart depicting the scope in context of suppliers, inputs, outputs, and customers

The SIPOC is useful to focus scope and to identify stakeholders. It is also useful in determining who has influence to make changes or improvements for the process in question. In this exercise, many levers were available to address the issues that were discovered during the value stream mapping process, but some were off limits. This corresponded loosely to the span of

control of the aseptic segment head which will allow for more effective implementation of the improvement plan.

4.2 Hypothesis Generation

Following scope definition, it is necessary to determine potential causes of the scheduling and process issues. First, a hypothesis tree was created to break down the high level concepts into precise and actionable tests. The hypothesis tree can be found in the appendix. As a case study, the hypothesis generation process started with a hypothesis such as "poor planning methods are causing write-offs". From there, this general hypothesis is broken into more specific and precise statements that can be tested. Continuing on this particular hypothesis, it was broken down as can be seen in the following figure:

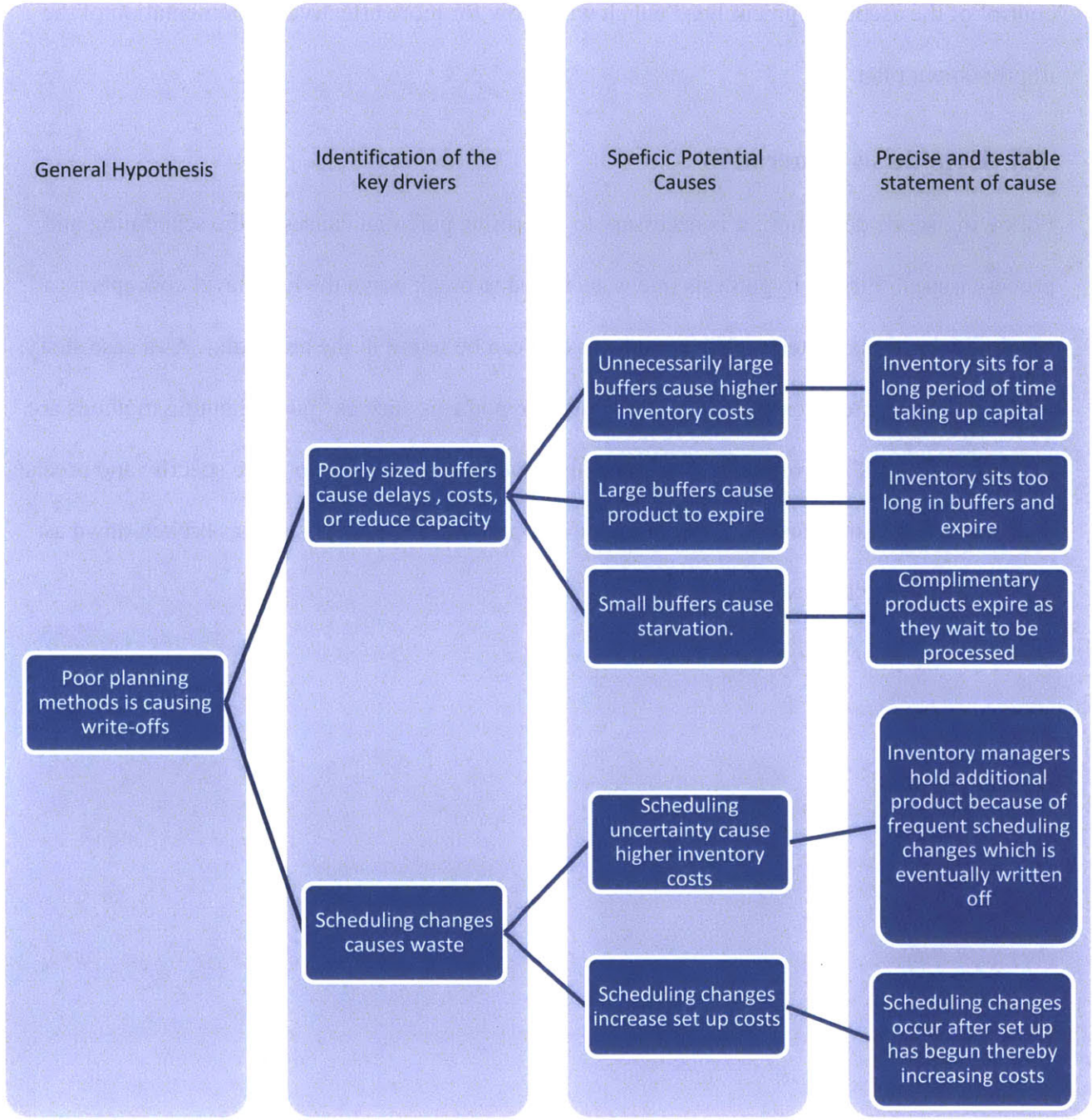


Figure 4: Hypothesis Generation Process

From the above figure, it should be noted the hypothesis transition from broad and general to the more specific and actionable. The mark of an acceptable hypothesis is if, after answering the question in either the affirmative of the negative, if there is a specific course of action that can be completed to fix the issue.

4.3 Project Baseline

This section will describe the initial state of the organization before the project began. It will help describe the motivations and need for the value stream map.

4.3.1 Current State of Data Collection

Data availability is critical to the successful implementation of a value stream mapping program. However, prior to this research, there was very limited useful data as can be seen in the below initial state value stream map representative of the Adjuvant Product Family (Figure 5). While the specifics of this chart are not of specific importance (nor legible in this format), it is useful to understand that red starburst indicate data that was not believed to be collected in any capacity and that yellow starbursts indicate where data is thought to be collected, but stored in a restricted or other difficult location that reduces its usefulness and accessibility. Larger starburst with improvement suggestions were placed to correspond and provide additional detail on the missing or lost data. In Figure 5, solid lines indicate product flow. Horizontal parallel lines indicate separate lines with parallel flow. Notched lines (those that look like lightning bolts) indicate electronic information flow and boxes represent process steps. Triangles indicate buffers and the circle with a U beneath it represents the number of personnel in that particular area. The notched line on the bottom (looks similar to the top of a castle) indicates value added time when the line is raised and non-value added time when the line is in the lower position.

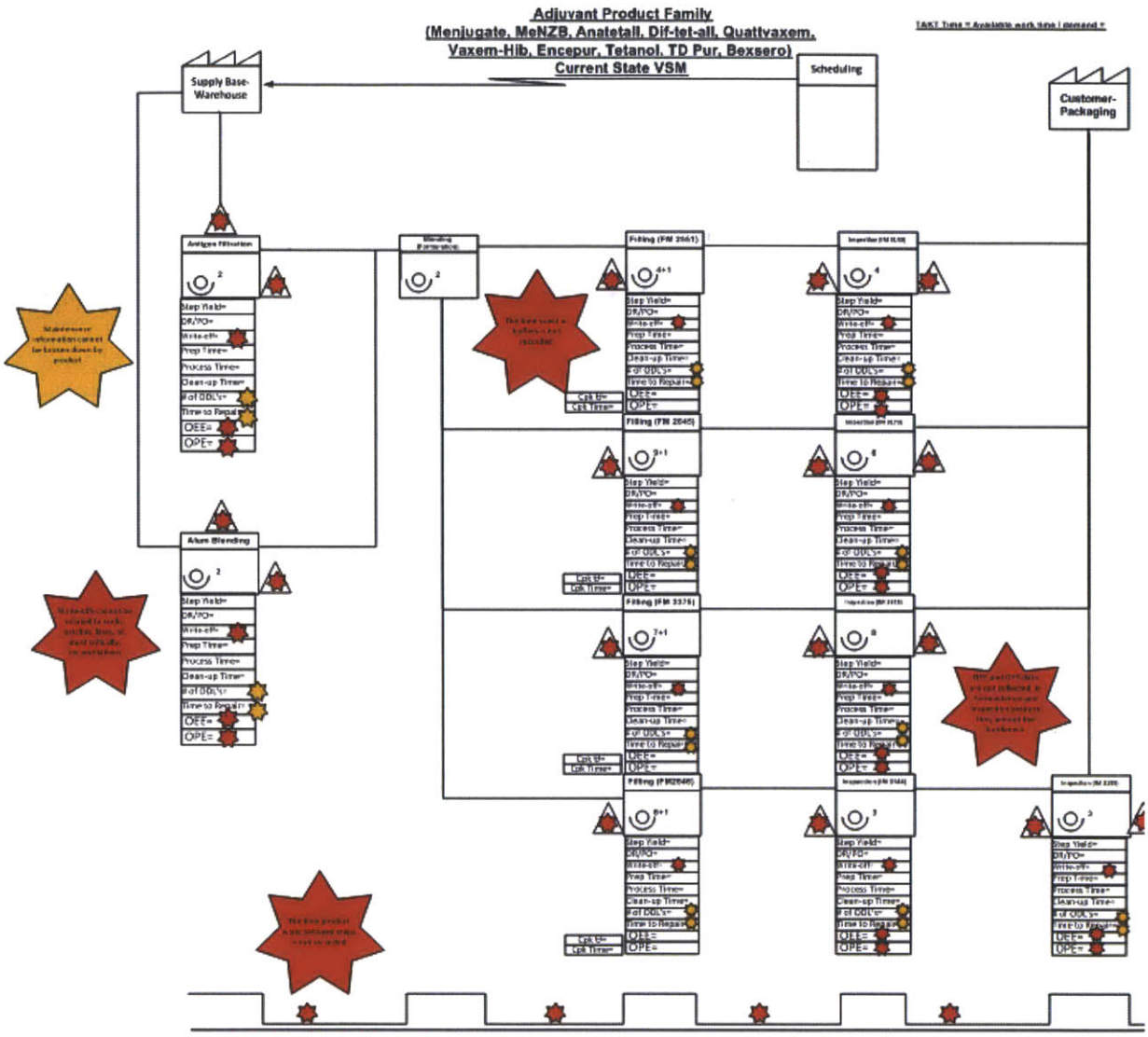


Figure 5: Initial State Value Stream Map Displaying Missing Data

However, senior managers believed that a lot of the necessary data was being collected. This disconnect had three major causes: the location of the data, a misunderstanding of what data is important, and the manner in which the data was presented.

1) Much of the data was stored on personal spreadsheets instead of companywide databases. While large data management software was employed, it was rarely used. In fact, often

times the data stored in the data management software, such as SAP, was incorrect and discounted. This led to those unfamiliar with the organization to use faulty data and for insiders to collect data on their individual computers.

Based on the research and through numerous interviews, one person had a good understanding of what data was collected and where. There were many instances in which one manager would state that a particular set of data was not collected only to have the next confirm that they did indeed have a spreadsheet on the computer. Conversely, it was discovered that the same data was collected by multiple sources, such as on a personal computer (or multiple peoples' computers) and in SAP. Often times, this data was not in agreement and left questions about accuracy.

The result of unorganized data collection leads to data being collected without a purpose and for those in need of data to analyze wanting. At first glance, data collected without a direct outcome does not seem to have negative repercussions. However, data collection, particularly in highly regulated industries such as the biopharmaceutical industry often requires additional work by the operators. Operators will likely stop collecting quality data if they do not see a benefit. Further, time spent on data collection is considered non-value-added time. That is, the time spent collecting data is not directly adding any value to the product and therefore should be minimized whenever possible. On the other hand, when data is not available, the opportunity cost could be high as potential improvements are foregone.

2) Because data collection decisions were often made the individual supervisor level, not at a plant or global level, often important data is missed. Each individual supervisor could fall into a tunnel vision that blinded them to potential improvements. For example, time

data was not collected for certain operations (particularly in the formulation stage) because the common believe was that the work done was too individualistic to be improved overall. However, it is expected that by learning the operation time and through analysis of trends, that best practices could be identified and spread throughout the plant and business.

3) Finally, data was rarely displayed to those who needed to use it in a coherent manner, such as the value stream map. It was therefore very difficult to use, compare, and assess the needs. Data and analysis would appear to more senior managers during meetings, but for those closer to the floor, it was rarely seen. In part because of this, each individual line and segments within that line collected data in different ways according to what they deem important and what is easiest for them: on separate spreadsheets, in nonstandard formats, and without common metrics.

4.3.2 Current Decision Making Process

Because of the above mentioned data collection issues that existed prior to the value stream mapping, there existed a culture of making decisions without analyzing the proper data. It was common for gut instinct, experience, and preference to be the basis for changes. However, this method contrasts directly with Lean, Six Sigma, and Novartis's own IQP (Innovation, Quality, and Productivity) guidelines for project management which state that data should be used to make all decisions [15].

4.3.3 A Culture of Data Hiding

Another significant aspect of the climate in the aseptic segment at Novartis Rosia was the manner in which data that indicates a potential for improvement was viewed. Managers saw data that indicated low performance as something that would be used against them, not as an

opportunity for improvement. Instead of using data to show how the segment could become better with potential rewards for improvements, it was seen as a cause for punishment and negative marks. Since standardized data collection was minimal, managers did not have motivation to display data that did not show their area of responsibility in a favorable light.

This manifested in managers not sharing their data with those who need to use it for proper analysis. Since the data collection was typically local and contained within the individual's computer, plausible deniability of the data existed sharing of the data could be prevented.

4.4 High Level Focus Factors

In order to confirm that the aseptic area had the most pressing write-off scenario out of all segments in the business, overall write-off data was examined. The below Pareto chart shows that the aseptic area (seen on the chart as "Tech Ops Aseptic") produces the most write-offs out of any department in the business.

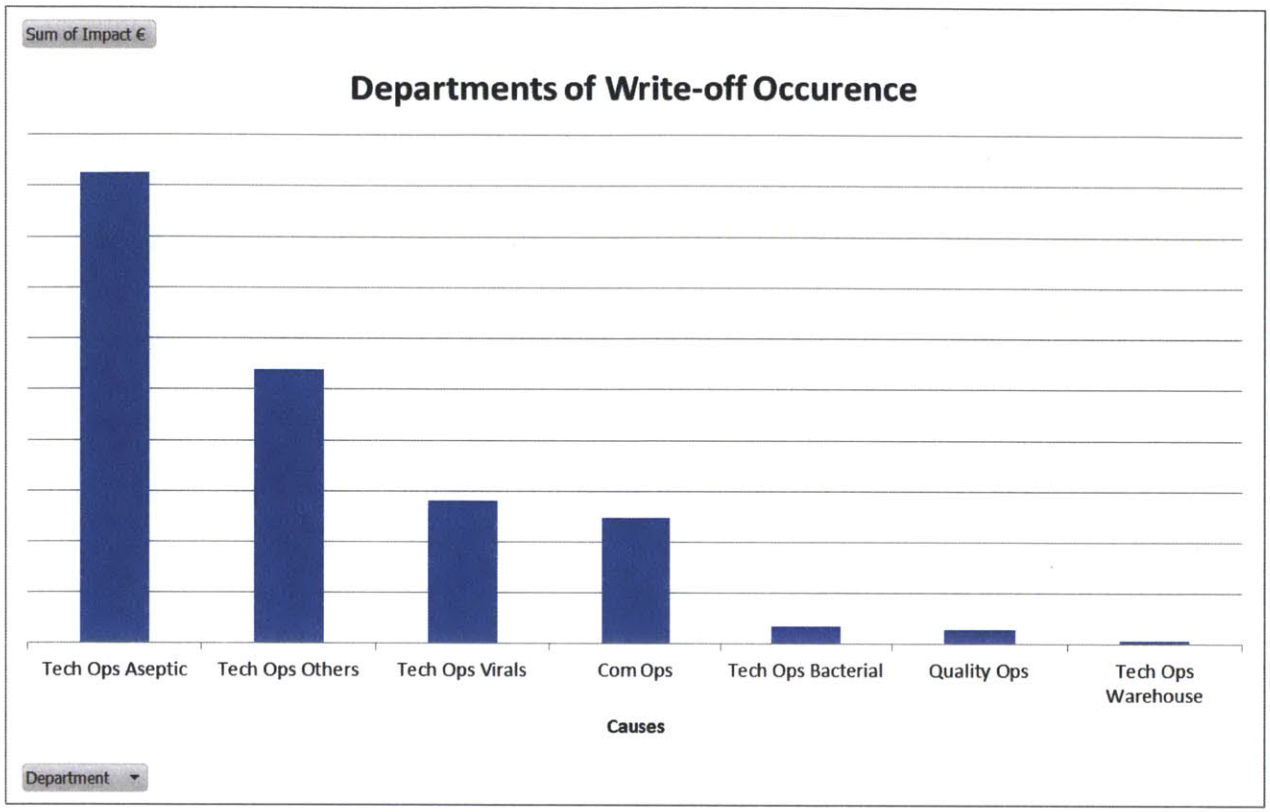


Figure 6: Write-offs Broken Down by Department of Occurrence

The next step was to break down the aseptic write-offs to determine their most probable causes. This served to provide a high level understanding of the source of the lost product. The following figure shows that contamination, bioburden, and sterility failures cause the most write-offs.

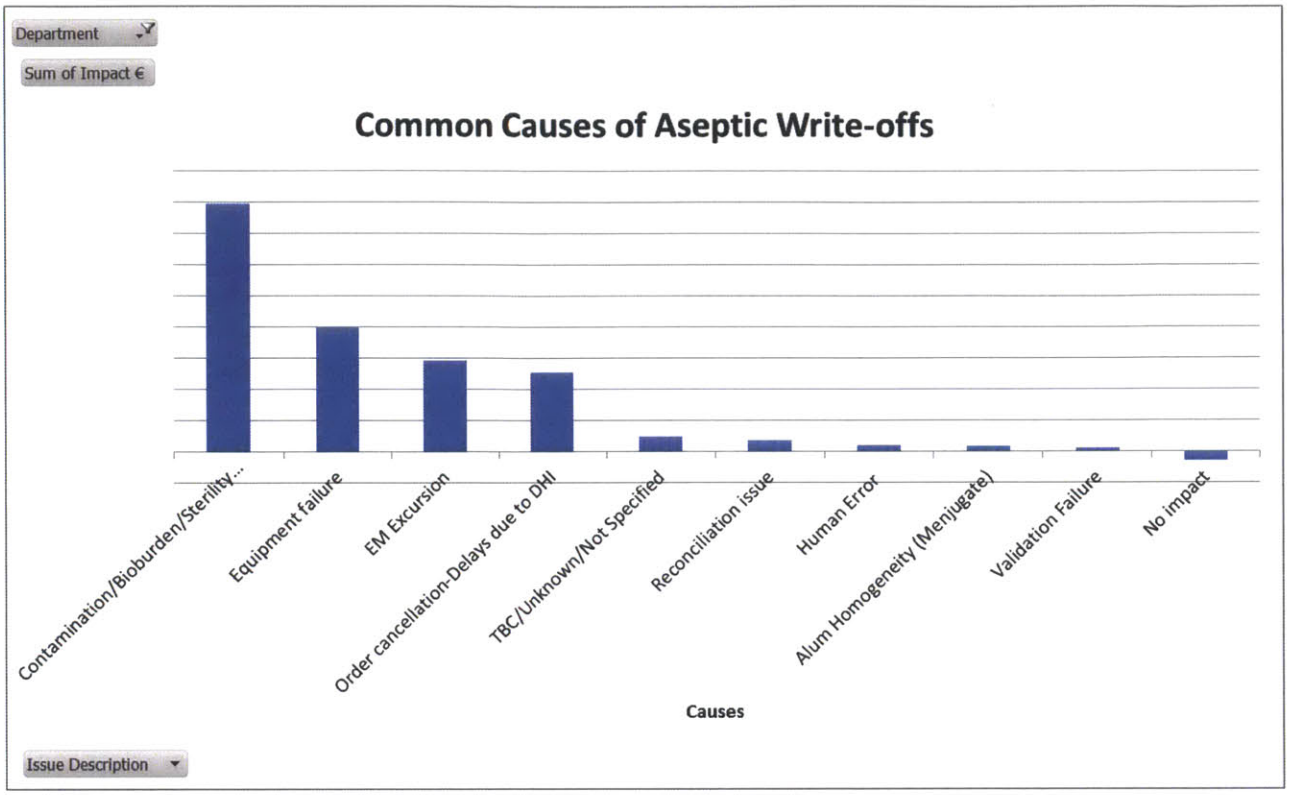


Figure 7: Leading causes of write-offs

It is interesting to note that the top three causes of aseptic write-offs are all directly related to process failures. This reaffirmed that value stream mapping was the optimal tool to determine potential improvements as the technique is able to readily show process failures. Another key observation from this chart is that human error ranks very low on the causes of write-offs. This is because many human mistakes are wrapped up into other categories. Human error is a large reason of issues with regards to the sterility of the process and the space, so it makes sense that the contamination, bioburden, and sterility category, along with the EM (environmental monitoring-measure of the sterility of the air in the aseptic space) excursions would outweigh the specific human error category.

5 Current State Value Stream Map and Analysis

This section is designed to display the findings from the value steam map and show the areas selected for further analysis.

5.1 Current State Value Stream Maps

Below is an example of one of the value stream maps created with starbursts indicating identified problem areas. Important sections will be highlighted below as Figure 8 is to provide a high-level overview

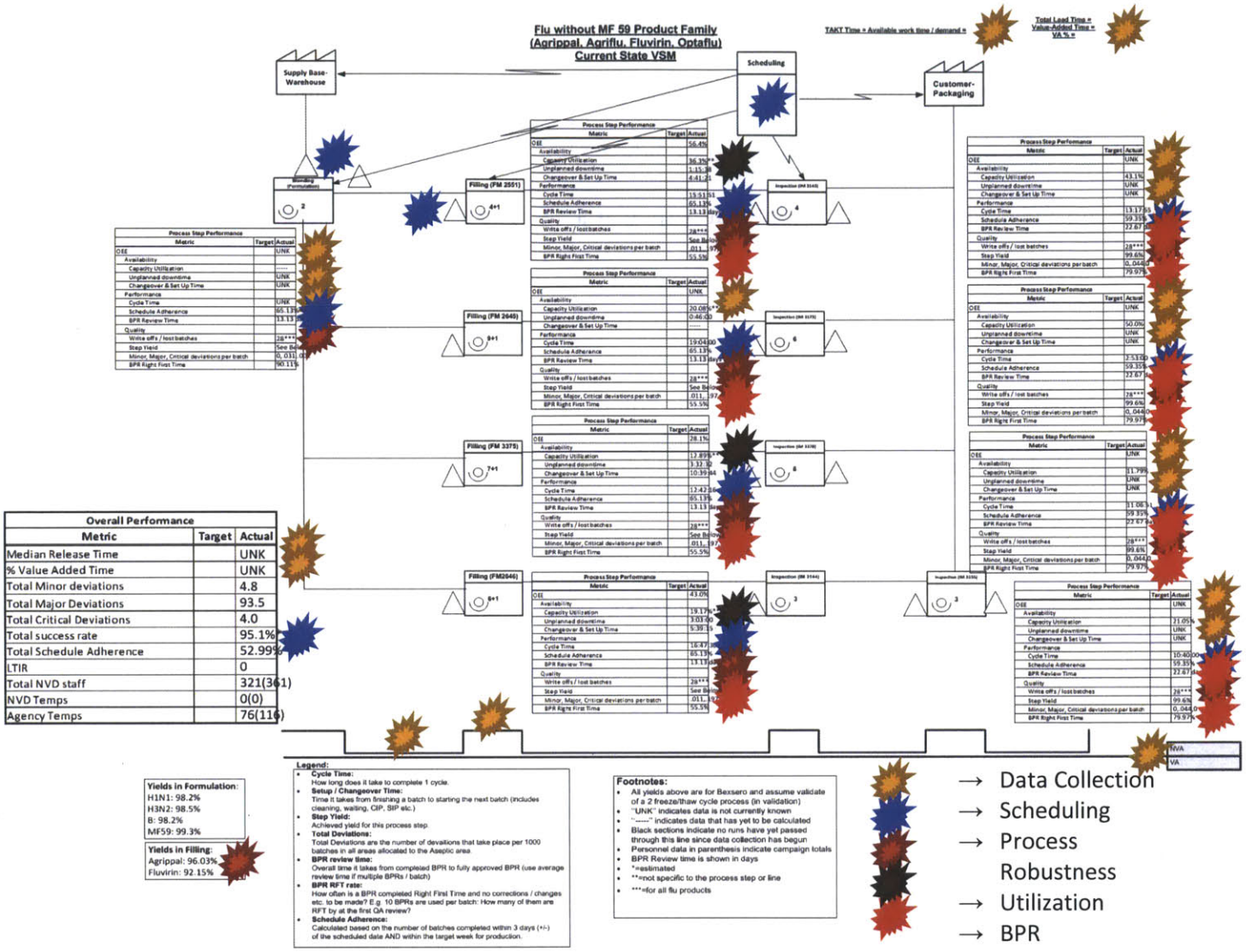


Figure 8: Current State Value Stream Map (Flu without MF59) with Issue Indicating Starbursts

The current state value stream maps served to aggregate all process data on a single location and to make a standard way to display data throughout the segments. Because of these value stream maps, a certain level of data is expected and that data can be easily compared to other similar segments and otherwise benchmarked. The current state value stream maps were also presented to many members of the aseptic area so all could see the data and their work. The figure above (Figure 8) shows an example value stream map of the flu product without the MF59 additive.

In this chart, similar to Figure 5, horizontal parallel lines indicate separate lines with parallel flow. Notched lines (those that look like lightning bolts) indicate electronic information flow and boxes represent process steps. Triangles indicate buffers and the circle with a "U" beneath it represents the number of personnel in that particular area. The notched line on the bottom (looks similar to the top of a castle) indicates value added time when the line is raised and non-value added time when the line is in the lower position. Additionally, the key on the bottom right of Figure 8 indicates the meaning for each of the colored starburst. For example, a red starburst indicates that a particular metric indicates a problem in the batch record review process.

In this map, the specific numbers are unreadable due to proprietary concerns. However, for the overall process, the following data box was filled to provide important overall performance metrics to the entire product family through the process. These data boxes were standardized throughout the company to make more uniform value stream maps.

Overall Performance		
Metric	**Target**	**Actual**
Median Release Time		
% Value Added Time		
Total Minor deviations		
Total Major Deviations		
Total Critical Deviations		
Total success rate		
Total Schedule Adherence		
LTIR		
Total NVD staff		
NVD Temps		
Agency Temps		

Figure 9: Overall Performance Metrics for Value Stream Maps

Additionally, the same information was collected for each step and line in the process as seen below:

Process Step Performance		
Metric	**Target**	**Actual**
OEE		
Availability		
Capacity Utilization		
Unplanned downtime		
Changeover & Set Up Time		
Performance		
Cycle Time		
Schedule Adherence		
BPR Review Time		
Quality		
Write offs / lost batches		
Step Yield		
Minor, Major, Critical deviations per batch		
BPR Right First Time		

Figure 10: Process Step Metrics for Value Stream Map

As seen in Figure 10, it was especially important to find information that is useful in the calculation of Overall Equipment Effectiveness (OEE) which meant focusing on availability, performance, and quality.

Similar maps were created for all product families and can be seen in the appendix. At a high level it was observed that the formulation stage of the process typically lacked data, that calculating percent value added time (a valuable component of value stream maps) could not be calculated due to a lack of time data, and that other issues fell into one of four primary categories: data collection, scheduling, process robustness, and utilization.

5.2 Analysis of Major Opportunities for Improvement

This section is designed to provide understanding of the four primary deltas that were observed in the value stream maps. Color coded starbursts are used in the above figure (Figure 8) to emphasize each particular category. A further breakdown of each category by line and product will be shown below.

5.2.1 Scheduling

The below charts show the schedule adherence metric for 2012 in the aseptic area broken down by both product and process step. Schedule adherence measures the ability of the process to manufacture a specific lot within three days of the scheduled production date as of the latest schedule revision.

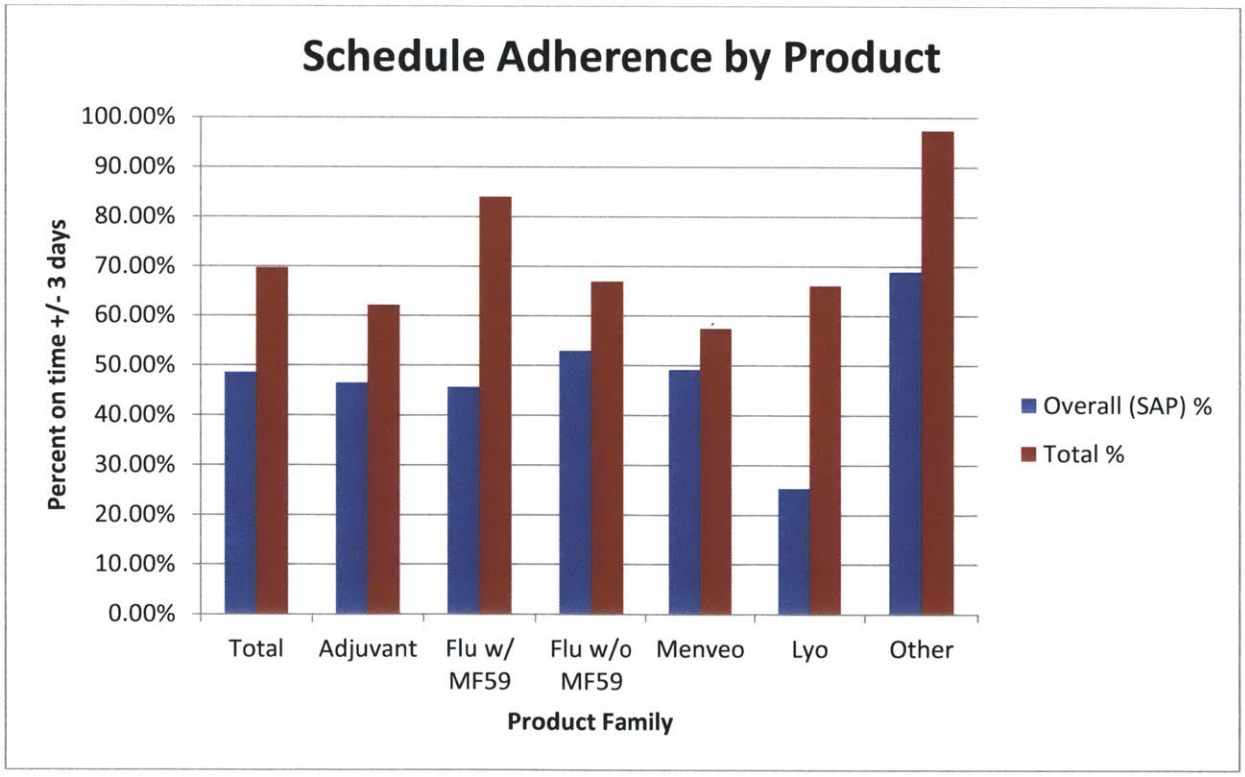


Figure 11: Schedule Adherence by Product Family

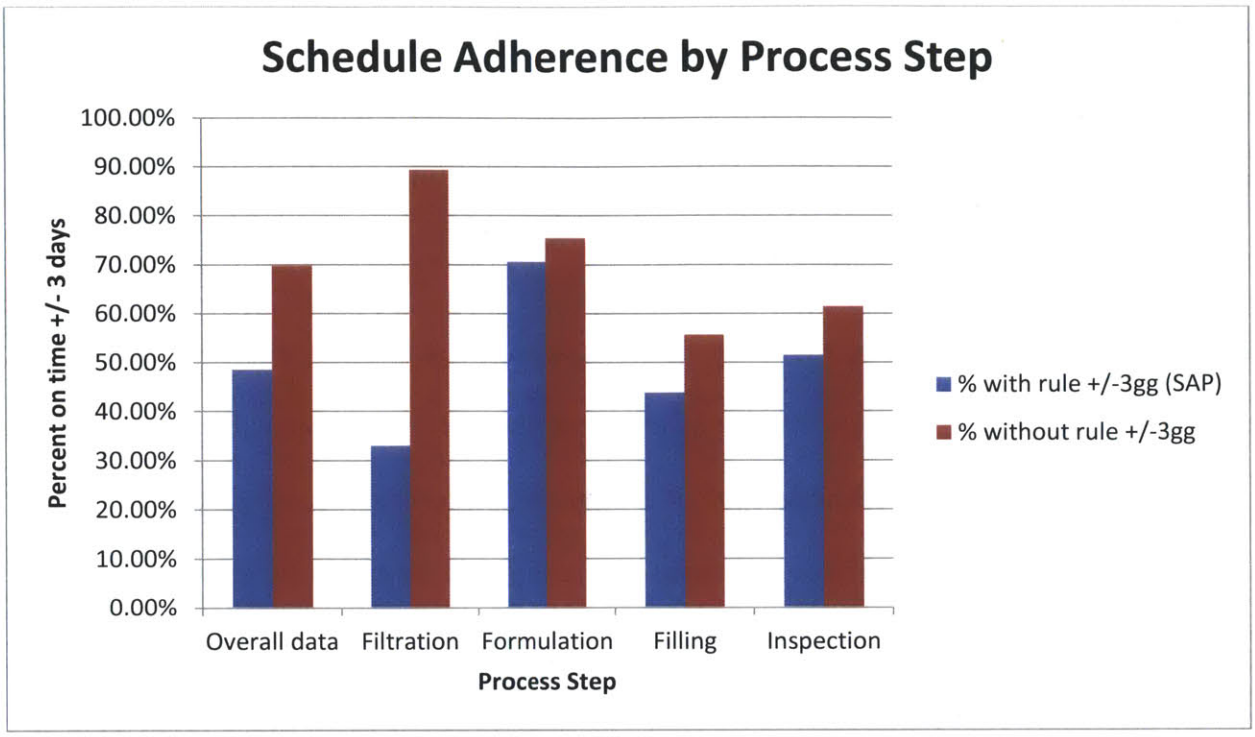


Figure 12: Schedule Adherence by Process Step

From these charts, there are two significant takeaways: low overall schedule adherence and differing results for the same process.

First, overall adherence is around 50%-70%, depending on which metric is used (to be discussed below). In other words, there is only a 50-50 chance that a scheduled batch will be manufactured within three days (before or after) of its intended date of production.

While all schedule adherence is low, it is interesting to note that the type of product and process step both have a significant effect on the schedule adherence. The data shows that campaigned products (primarily both flu families) typically have a better flow than those that are not produced in campaign. As flu products are the only products produced in large scale campaigns, it can be seen that their respective schedule adherences are both higher than average.

Additionally, since filling and inspection are often run continuously on the same line, their adherences are similar, but lower than that of formulation. Variation in the formulation process (including variation due to lower adherence upstream) is a cause of the low adherences in filling and inspection.

Second, there are two methods of analyzing the data that show significantly different results. This illustrates the before-mentioned data collection and data perception issues that resulted in employees having private spreadsheets on their computers that complemented what is on a larger database. In this case, SAP measures adherence differently than the employee responsible for this metric. While the employee's method seems to be more correct based on an independent overview of the methods used to obtain the data, the formula in SAP has not yet been corrected, so only he has the correct information which severely decreases the data's usefulness. The red bars (typically higher than the blue bars) are from the employee whereas the blue bars are extracted directly from SAP.

These scheduling delays have negative consequences because disrupt labor planning, cause materials waste, and cause an inconsistent output to the downstream manufacturing steps of packaging and labeling. Operators are told of their schedule based on when their services are required (different products have unique labor requirements) so a change in product can change a schedule. This decreases employee satisfaction and increases frustration with the system. Additionally, since changes are often made at the last minute, many materials (such as the piping in formulation) have already been prepped for production by the time the change is made. Once the set-up created, it much be used in a timely manner, or in the case of a schedule change, scrapped. Finally, when conducting interviews with the aseptic segment's downstream customer, the packaging segment, the chief complaint is that their operations schedule in a

constant state of flux due to the inconsistent output from aseptic which causes their production costs to increase.

5.2.2 Process Robustness

Most employees, supervisors and operators alike, believe that deviations are the cause of many of the problems in the aseptic area. The data supports this observation in that deviations are very common in the process. A deviation report is filed every time anything in the process deviates from what is certified and planned. There are three levels of deviation (minor, major, critical) depending on the severity of the deviation. The below figure shows the breakdown of deviations by type over the first seven months of 2011.

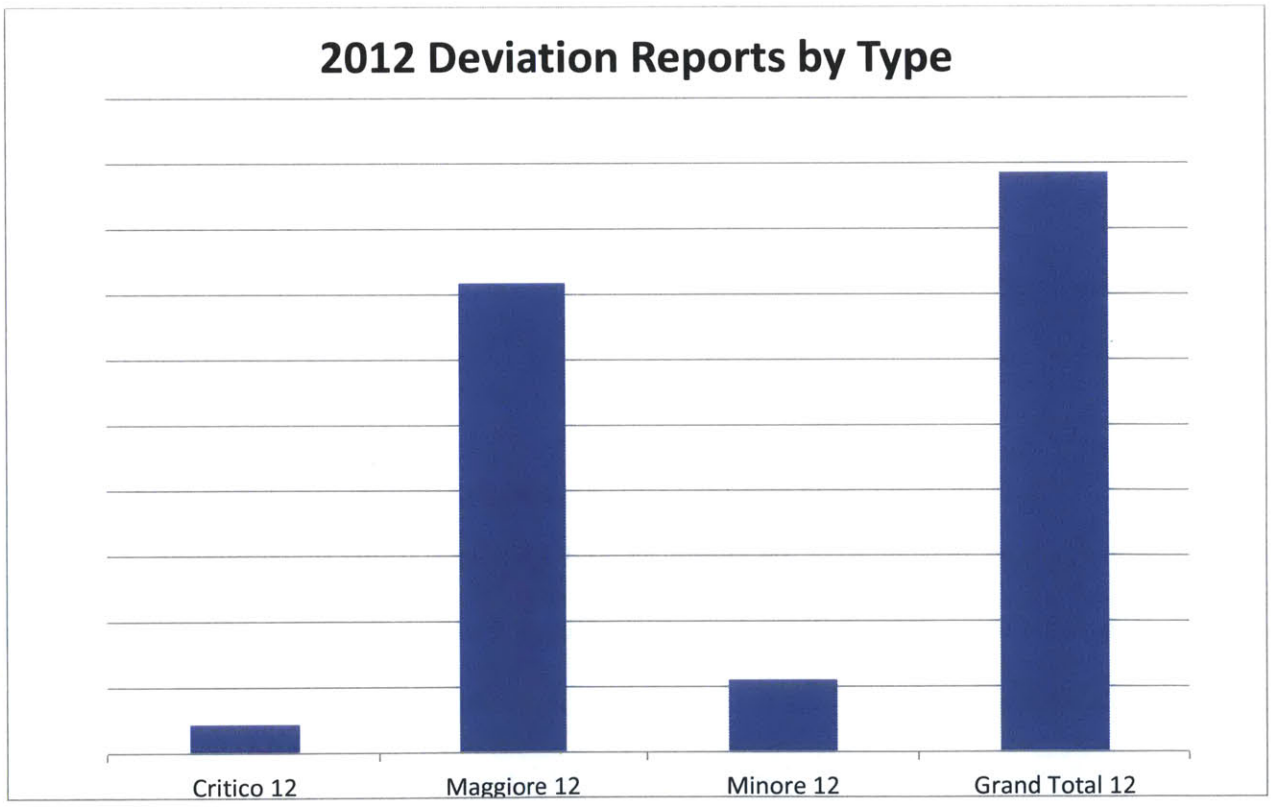


Figure 13: Breakdown of Deviation Reports by Type

From the above figure it is interesting to note that major deviations are expectedly much more common than critical deviations, but unexpectedly more common than minor deviations. The response procedures for critical and major deviations are much more complex making this observation concerning. Going a level deeper, the below figure shows the number of deviations, by type, over the first 7 months of 2011 and 2012.

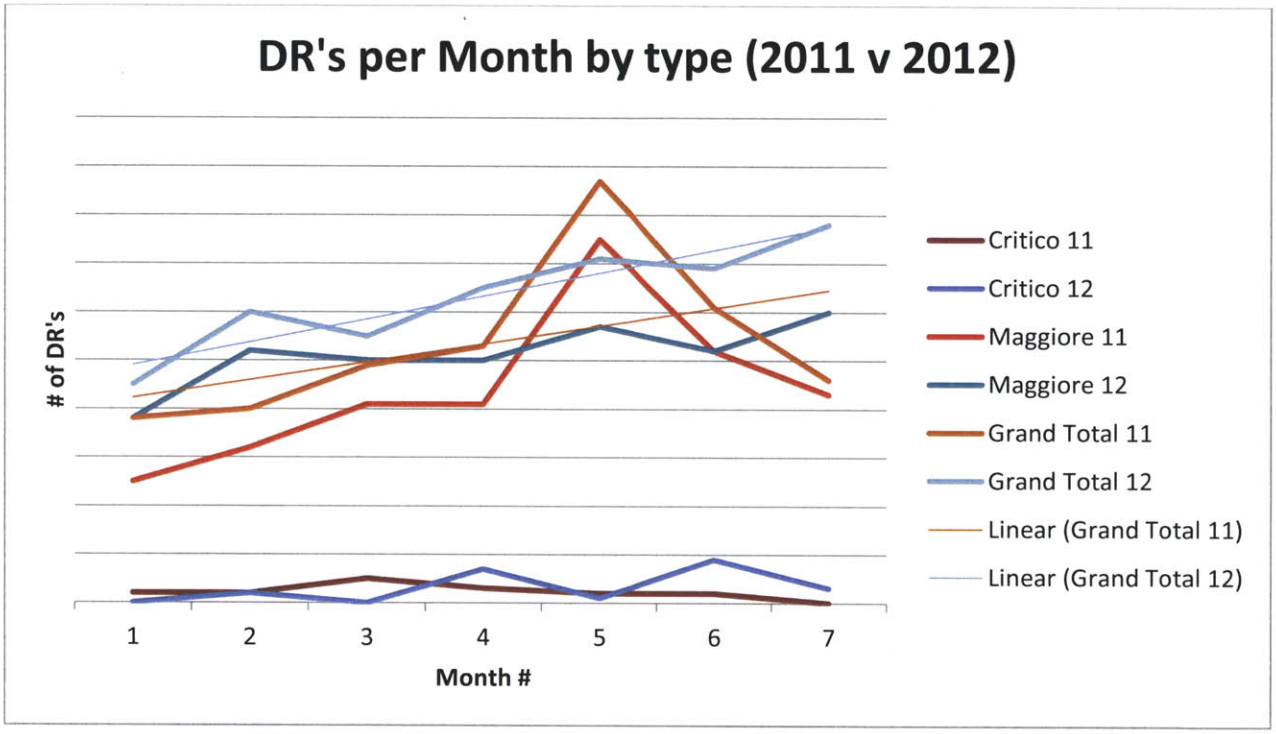


Figure 14: Breakdown of Deviation Reports by Type over Time

The above chart shows that, in 2011, deviations spiked at the start of the flu campaign corresponding with an increase in throughput, but lessened as the campaign increased in duration. In 2011, great attention was paid to this rise in deviations and therefore, with learning, the number of deviations decreased. Conversely, in 2012, because of numerous urgent external issues, personnel and resources were removed from the segment and therefore knowledge and expertise was lost and the learning did not occur in 2012.

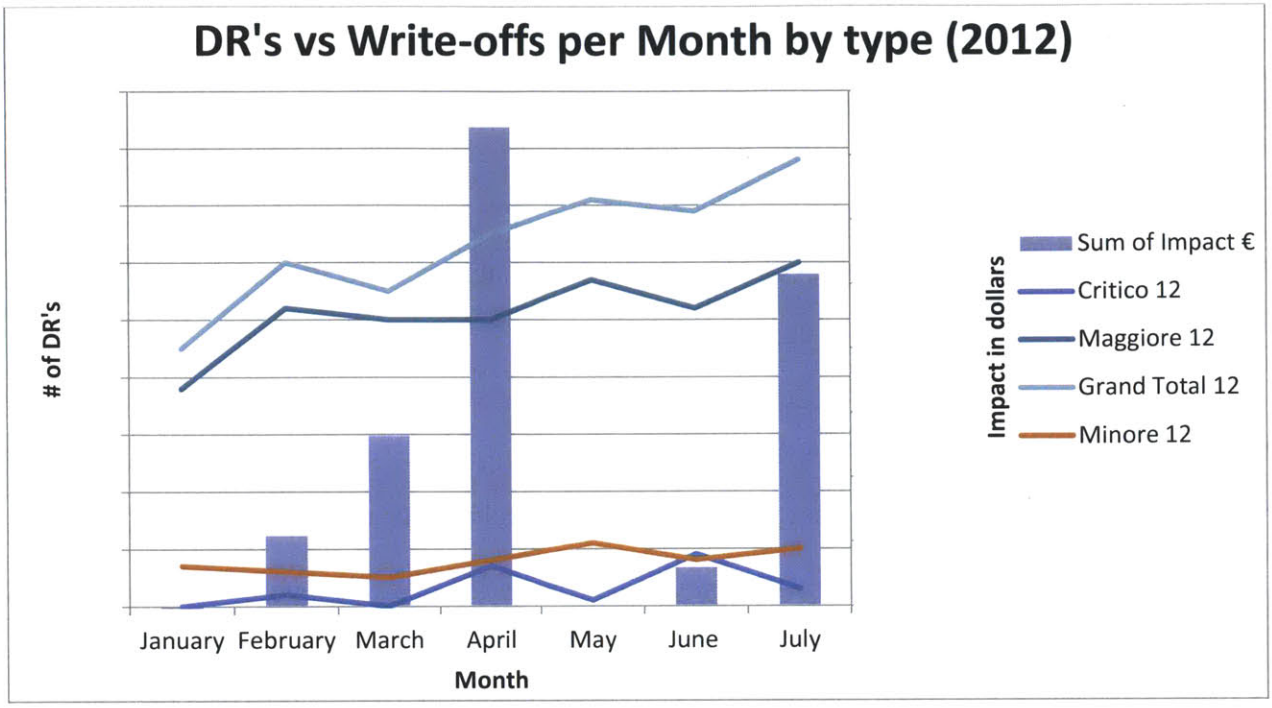


Figure 15: Write-offs by Month

The above chart can be used to test the hypothesis that deviations are a cause of write-offs. In the chart the bars indicate the amount of each type of deviation for each month. "Critico" indicates the number of critical deviations, "Maggiore" indicates the number of major deviations, and "Minore" indicates the number of minor deviations in a given month in the aseptic area. Due to scale, both January and May appear to be zero; in actuality, both these months had write-offs near, but not exactly, zero. This is because a large amount of product that was reinstated in comparison to what was written-off in those particular months. While there are not enough data points to perform a multivariate regression, it does appear that there is a moderate correlation of .368 between the number of critical and major deviations with the write-offs for that particular month (as product is accounted as written-off very shortly after a deviation occurs, but can be reinstated if the deviation is repaired). This correlation increases to .400 if minor deviations are

excluded. From this, the conclusion that increased deviations, particularly major and critical deviations, are a cause of increased write-offs can be drawn.

5.2.3 Process Efficiency

This section will show the low process efficiency with two metrics: utilization and overall equipment effectiveness.

5.2.3.1 Utilization

Poor schedule adherence and constant process problems preclude the aseptic process from running at it full efficiency. Process efficiency was measured in two ways: with the utilization metric and with overall equipment effectiveness (OEE). It is important to note that there is no utilization or OEE data for formulation because time data is not collected in the formulation division based on the incorrect theory that the process is too individualized to be improved. Additionally, insufficient data exists to measure the OEE for the inspection lines and for Line 2's inspection utilization and OEE. The below figures (Figure 16: Utilization for each Inspection Line and Figure 17: Utilization for each Filling Line) show the utilization of each of the filling and inspection lines.

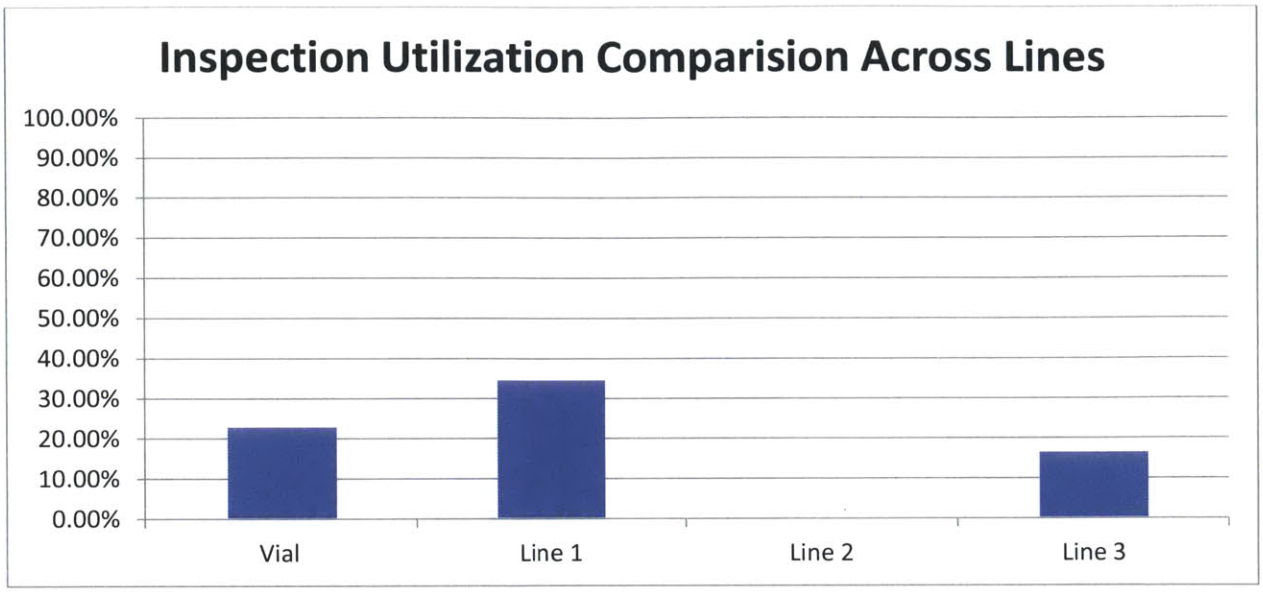


Figure 16: Utilization for each Inspection Line

As can be seen in Figure 16, the inspection utilizations are very low, in part because the inspection machines follow the bottle neck in the process, the filling machines. Since the rate of the inspection machines is much greater than the machines that precede them, the inspection machines experience starvation. Starvation can occur when processing rates of individual machines are different or if there is an improper amount of work in progress. This means the inspection machines have non-value added time in which they are not be utilized waiting for product meaning that expensive capital assets are being left idle and not being used to their full potential.

Utilization is defined by the number of syringes or vials that were produced divided by the number that could theoretically be produced. In this case and below in Figure 17, production refers to the number of units inspected, production refers to the number of units filled. The number of units produced was determined by examining the production records while the theoretical maximum number of units that could be produced was determined by finding the number of working hours per day multiplied by the certified production rate.

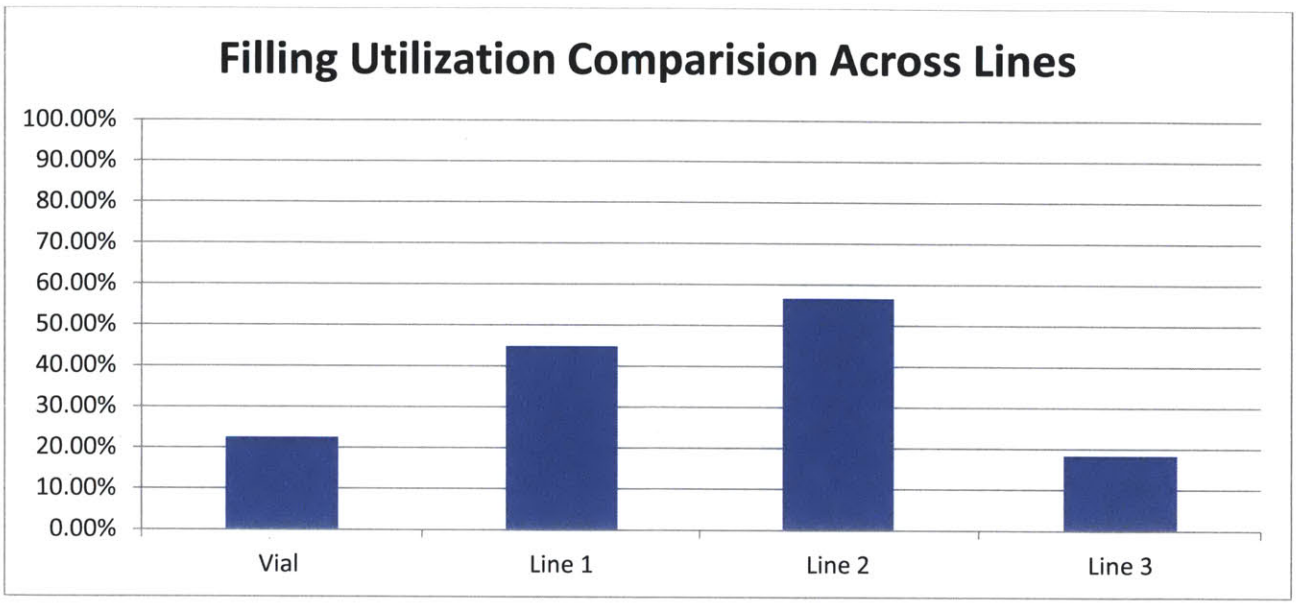


Figure 17: Utilization for each Filling Line

Filling utilization was calculated based on the theoretical number of units that could be produced compared to the actual number of units produced, taking into account time lost due to breaks, meals, and meetings. The biggest single reason for the low utilizations, however, was running the machines at substantially less than validated speed. The filling machines are running, on average between half and three-quarters of their approved speeds. Throughput could in greatly increased by finding and addressing the root cause of the slow machine speeds. The initial hypothesis is that the aging machines are no longer able to keep high speeds because a lack of preventative maintenance or simply because the machines are relatively old. According to aseptic managers, the amount of additional product that would be written-off running at high speeds would be greater than any incremental profit gains. Since the vaccines are typically not demand constrained (meaning that there is more demand than supply), increasing throughput should directly increase revenue and profit.

5.2.3.2 Overall Equipment Effectiveness

Another measure of system performance is overall equipment effectiveness. This metric is defined by Novartis Vaccines as "a total measure of performance that relates the availability of the process to the productivity and quality" [15]. OEE takes into account the availability, performance, and quality of the process. Availability takes into account equipment breakdowns and set-up/adjustment times, performance measures process speed and small (micro) stoppages, and quality looks at the defect rate along with other losses that lead to reduced yield (such as startup losses stoppage losses). The below figure also illustrates these factors relationship in the metric [15]. For example, starvation would cause stoppages and decrease the "performance" metric.

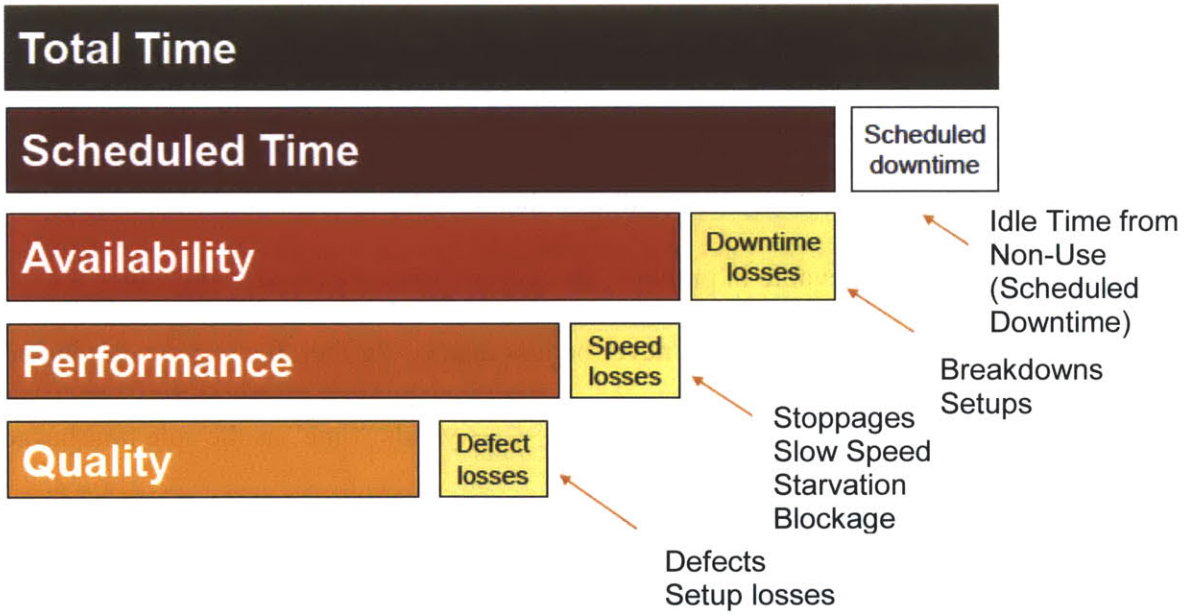


Figure 18: Visualization of Overall Equipment Effectiveness

The actual formula for OEE is as follows:

$$OEE = Availability \times Performance \times Quality$$

Equation 1: Overall Equipment Effectiveness

and can be broken down as follows with each of the three metrics of OEE (availability, performance, and quality) is bounded by 0 and 1:

$$\frac{Scheduled\ Time - Downtime}{Scheduled\ Time} \times \frac{\#\ of\ Units\ Produced\ \times Ideal\ Cycle\ Time}{Actual\ Runtime} \times \frac{Input - Defects}{Input}$$

Equation 2: Overall Equipment Effectiveness Formula Breakdown

Where "scheduled time" is the time during which the equipment was expected to operate, "downtime" includes breakdowns and set-up and clean-up time, "# of units produced" refers to the number of units produced in a cycle, "ideal cycle time" is the designed cycle time, "actual runtime" is the scheduled time minus downtime, "input" is the number of units that started the process, and "defects" is the number of defects (including those that underwent rework to be salvaged). The middle term above is the most complicated and should be thought of in terms of a shift with the numerator being the minimum (best theoretically possible) amount of time required to produce the units produced in that shift and the denominator being the time of production. The numerator provides the minimum theoretically possible runtime possible and since this number is not achievable in practice, the term will never exceed 1 and, since the product cannot be negative, the term will never be less than 0. Further, the term is dimensionless as the numerator's units are time ($\#\ of\ units * \frac{Time}{\#\ of\ Units}$ yields "time" as the sole unit because the "# of units" terms cancel) and the denominator, runtime, is also in time. OEE is commonly expressed as a percent by multiplying the final value obtained from the above formula by 100. Because OEE is the product of three factors, the OEE score will be lower than any single metric. The OEE for the Rosia Aseptic area's filling lines can be seen below.

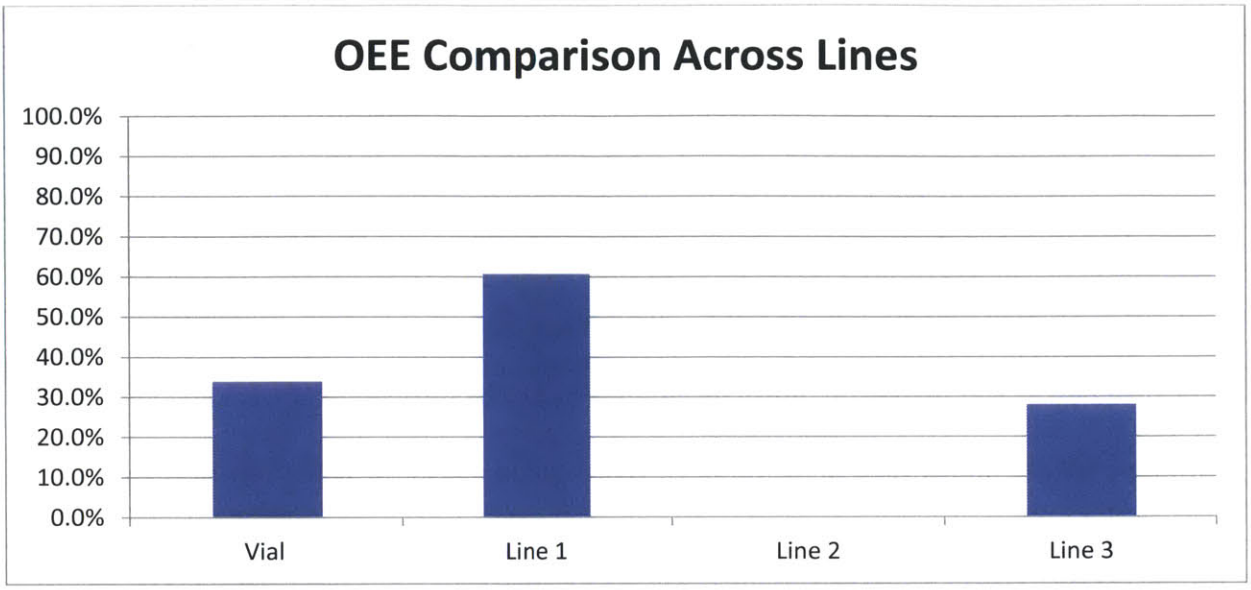


Figure 19: OEE for the Aseptic Filling Lines

As can be seen from the above figure, OEE's are much lower for the vial line and line 3. One significant factor is that line 1 is typically run around the clock operation whereas the other lines are not. This reduces urgency and causes line 1 to be prioritized to ahead of the other lines.

5.2.4 Batch Record Process

The batch record review process is the final major problem area identified in the value stream map. Batch records are one of the most critical operations for manufacturers of biopharmaceuticals as they are mandated by the FDA and other ministries of health. They are to be a complete master production record for each batch that is produced. A batch is defined by 21 CFR Part 210 as "a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture." This means that multiple batch records must be generated each day since multiple batches are being processed within the aseptic plant. According to good manufacturing process, a batch cannot be released for sale until the batch record is completed and certified [16].

Because products cannot produce revenues until the batch record is completed, it is vital that there be a good process in place to ensure that they are completed correctly and efficiently. There are two primary metrics that are used to describe batch record review (BPR) performance. The first one is "right first time" which is typically expressed as a percentage of batch records that make it through the verification process without requiring rework. Because each correction much be made by a specific person, mistakes often prove to be difficult to correct and add significant non-value added time to the process. The second metric is "batch record review time" which measures the amount of time from the start of the process until the batch record is completely approved. There are many reasons that review times are higher than desired including poor quality/production integration and batch records requiring rework.

In general, the research found a direct relationship between the review time and right first metrics. This is displayed in Figure 20 below.

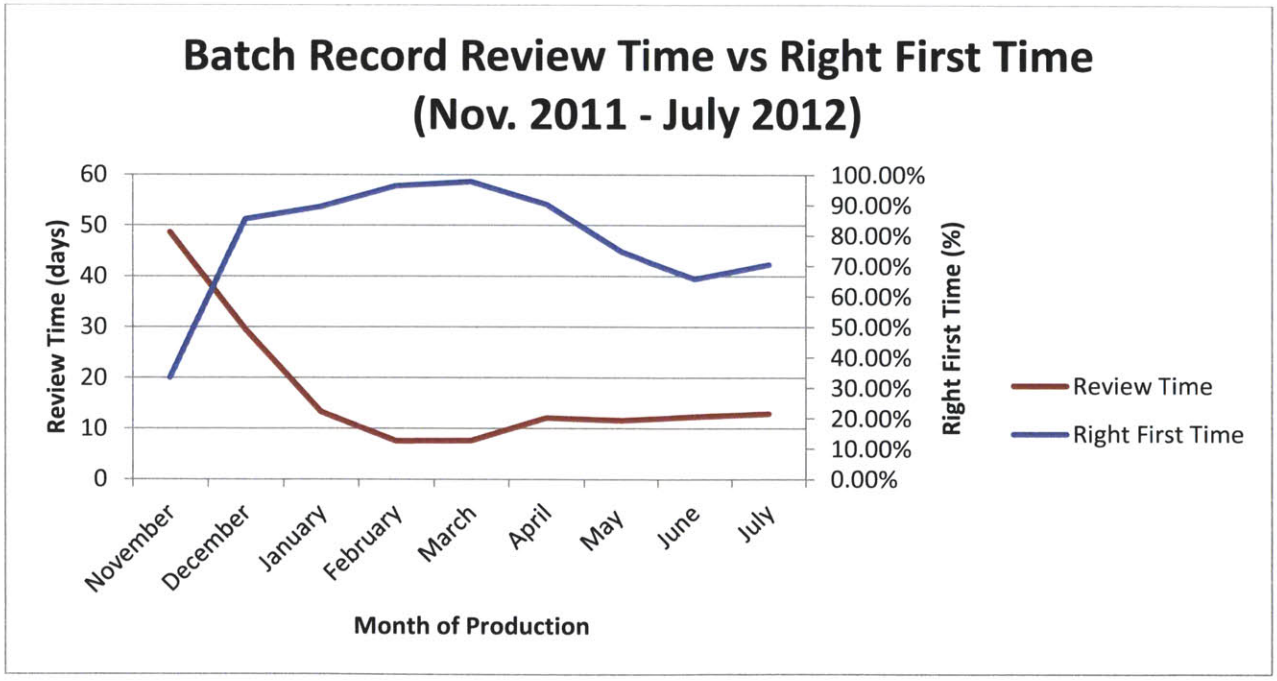


Figure 20: Batch Record Right First Time vs. Review Time by Month

This pattern is also repeated, though not as strongly, on a product by product basis as seen in the below figure.

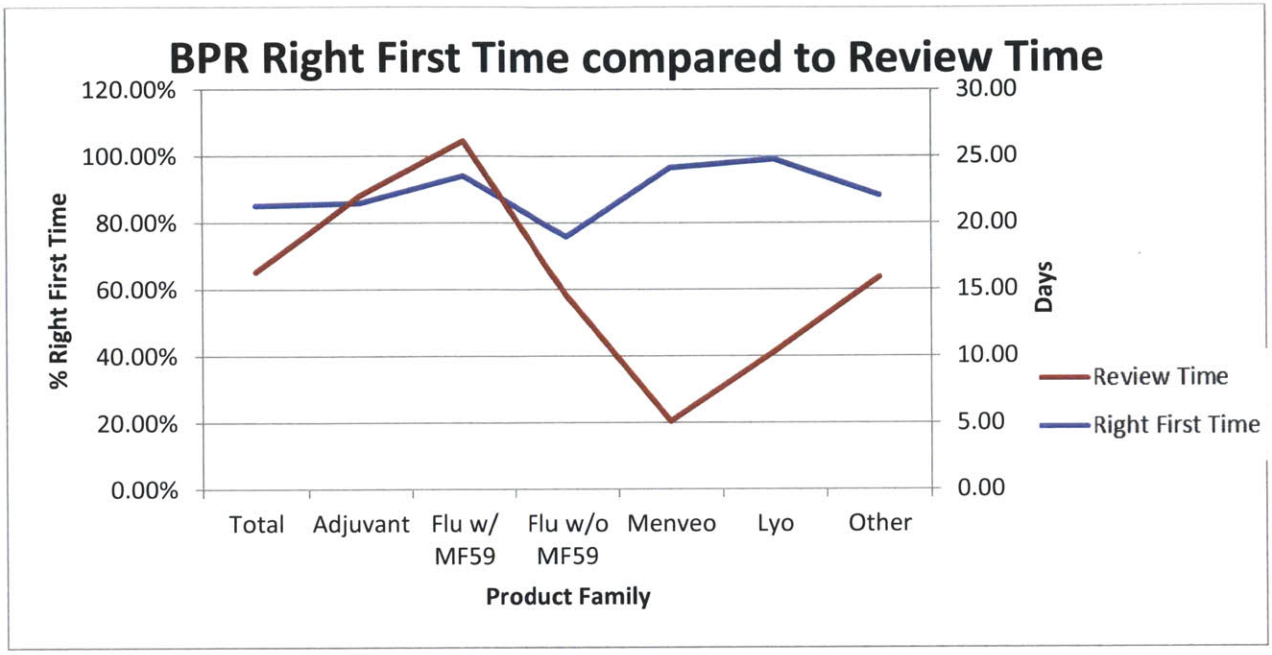


Figure 21: Batch Record Right First Time vs. Review Time by Product

This relationship indicates that the primary reason for long batch record review times is rework and a poor rework process. The high right-first-time rates are achieved by adding additional reviewers in the process so that it is unlikely that an error would pass to the quality assurance reviewer. However, because this is just lengthening the process, it causes the review time to never decrease to goal levels (one day). Even the minimum acceptable level of one week is not met during any month indicating that there are both process and rework process failures.

The data therefore indicates that, in order to solve these two correlated metrics, alternate methods must be used as increasing inspection layers during the review process does not solve both issues. A potential solution is to better integrate quality during the batch record creation. Instead of having quality assurance (QA) act as an outside organization, they should partner with

production as the document is being drafted to prevent mistakes while it is easy to correct them, as opposed to waiting until the draft is completed.

The data can also be viewed by process step as seen below in Figure 22.

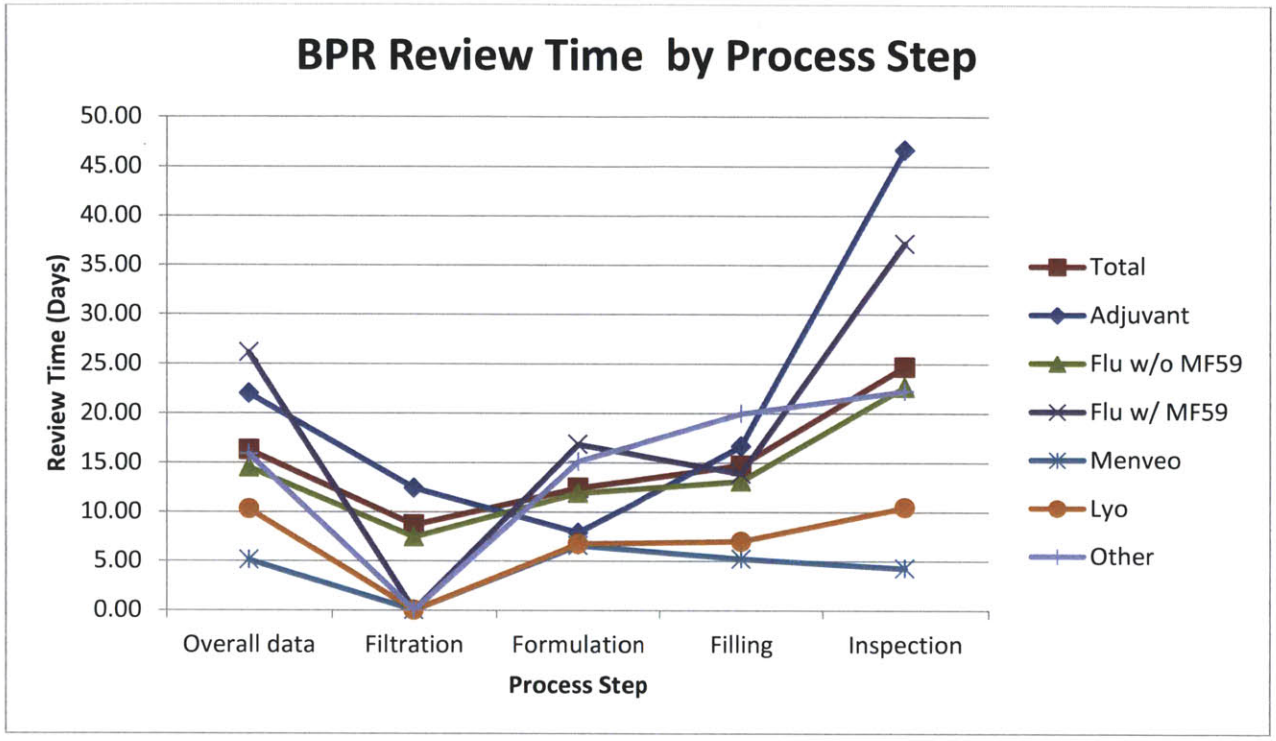


Figure 22: Batch Record Review Time by Process Step

There are two important takeaways from this chart. First is that Menveo does not follow the same pattern as the other products. This is because Menveo is seen to have a higher value (because of its higher margin) and is therefore prioritized above all other products. This further indicates that the current review process cannot handle the volume of batch records that must be handled.

The other major takeaway is that the farther a batch is into the process (for example: inspection vs. formulation), the longer the review time for that process step's batch record. Unfortunately, this is the worst time for the delays as the product has a higher worth as it gets closer to

completed which increases holding costs. Additionally, because late delays are more likely to cause a delay in shipment since they occur closer to the ship date, there is an opportunity cost of missed revenue.

5.3 Root Cause Analysis

After investigating the primary issues, the next step is to identify the root causes. The below diagram was created to link the symptoms to their underlying effects. This diagram was created by showing the symptoms and their underlying problems on the same page, then linking causes and effects to show relationships.

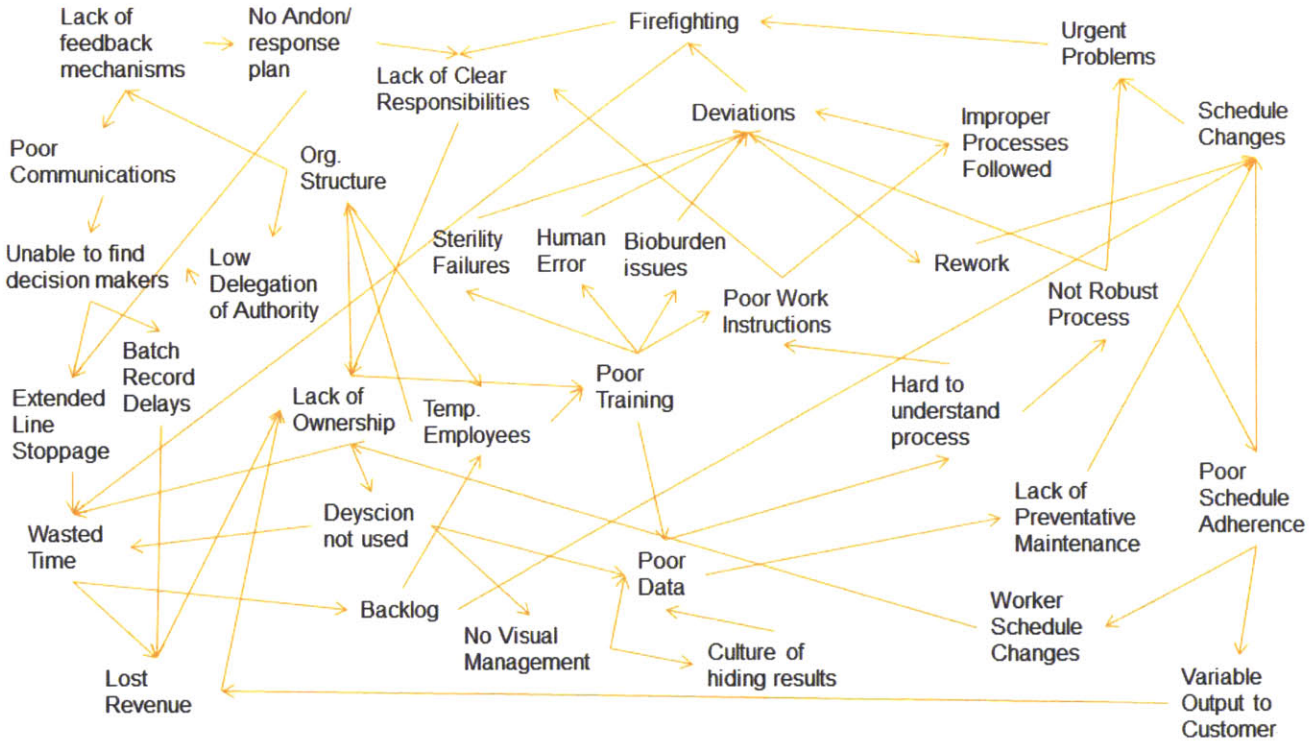


Figure 23: Interconnected Nature of the Current Problems

The above diagram shows that many of the symptoms that are seen in the process (such as insufficient data collection, poor schedule adherence, too many deviations, batch record delays, and process inefficiencies) have similar underlying issues such as a lack of feedback mechanisms

in the process and from worker to supervisor, poor communication of goals and current state, and insufficient training. It was found that, while it is good news that the issues are interrelated, large companies such as Novartis expect to see immediate results and often do not have the "patience" to attack the underlying issues. Figure 23 presents the argument that in order to make the changes that will have large scale immediate results; the underlying organization issues must be first addressed.

In this diagram it can be seen that there are many issues in the process, with one of the most significant being scheduling. This manifests itself in the blockages and starvation (Figure 19 shows the low filling lines for the process which are, in part, attributed to blockages and starvation). Additionally, the scheduling issues seen as the work in process inventory is very high and because product spends a large amount of time in queues (product has been scrapped because inventory sits in queue past its expiration date) and because cycle times are very high (weeks are allotted for a one day process). This process cannot be fixed by tweeking parameters or changing an algorithm, but must be addressed through cultural change. This cultural change will, as is shown in the following sections, needs to address to feedback, communications, and other fundamental issues before directing making changes to the scheduling process.

5.4 Issue Prioritization

To sort the problems facing Novartis and provide an actionable plan of attack, the improvement projects need to be prioritized against a common metric, in this case an adaptation of the United States military's CARVER matrix [17].

5.4.1 The CARVER Matrix

The goal of the CARVER matrix, in the military sense, is to "achieve victory by inflicting the greatest damage on your enemy with the least amount of resources" [17]. Similarly, in the biopharmaceutical environment, the goal is to produce the greatest number of vaccines to help patients with the lowest cost. In this case, cost includes monetary costs, resource utilization, human capital utilization, and good-will costs. In other words, this framework is designed to prioritize to achieve the highest efficiency, leanest process possible [17].

The adapted elements of the CARVER matrix can be seen below in Figure 24.

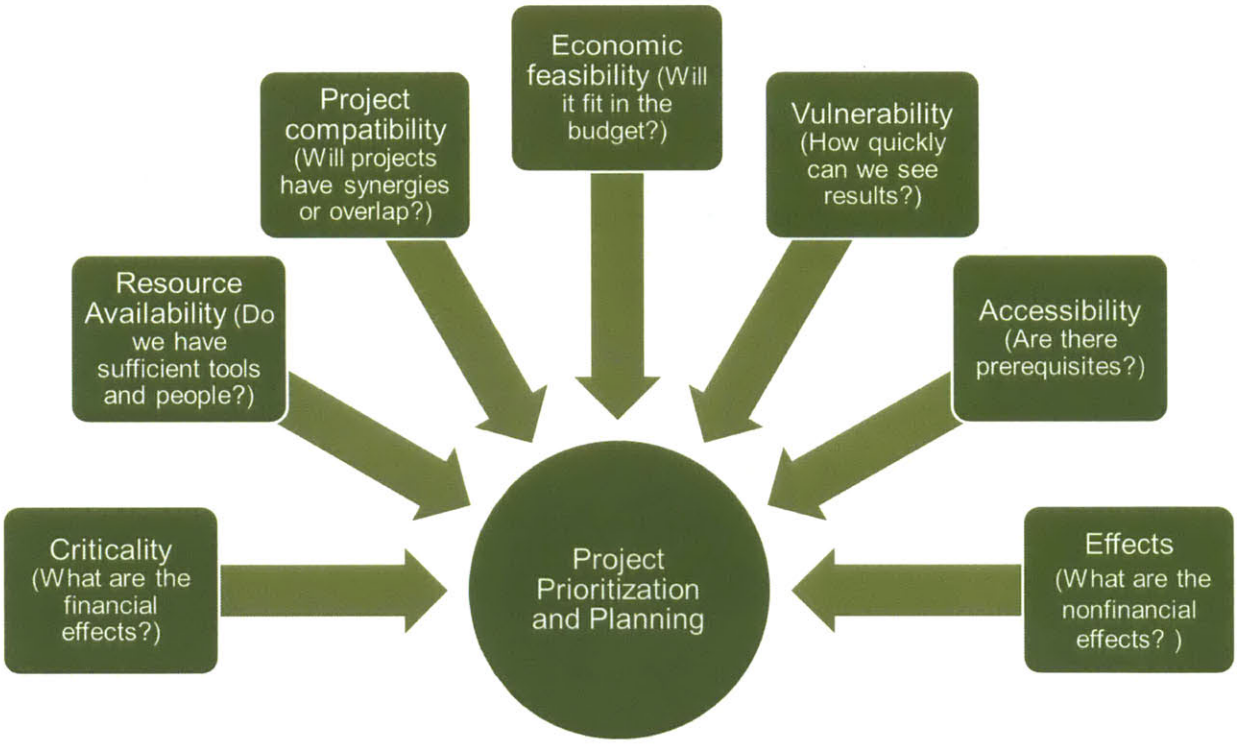


Figure 24: CARVER Matrix for Prioritization Adapted for the Biopharmaceutical Industry

5.4.2 Application of CARVER Prioritization

Once defined, the elements need to be applied to the results from the value stream mapping exercise. Cause and Effect Matrices were used for this purpose in which each project was assigned a score corresponding to each of CARVER's seven elements. In each matrix, each of

the factors was assigned a relative importance to the other factors. For example, "effects" had a higher priority than "accessibility" and therefore a high score in "effects" carries more weight than one in "accessibility". The matrices were broken into projects with long term horizons that had short term prerequisites and those that needed to be (or could be) completed in the short term. The matrices can be found in the Appendix.

5.4.3 Prioritization Results

After each project was evaluated on the based on all seven dimensions, they were prioritized as seen below in Figure 25 and Figure 26. The prioritization graphs were an output from the cause and effect matrices produced based on the CAVER prioritization analysis. In the cause and effect matrix, each factor was multiplied by its relative importance and then summed across the project to determine a final prioritization score which was, in turn, used in the creation of the prioritization graphs.

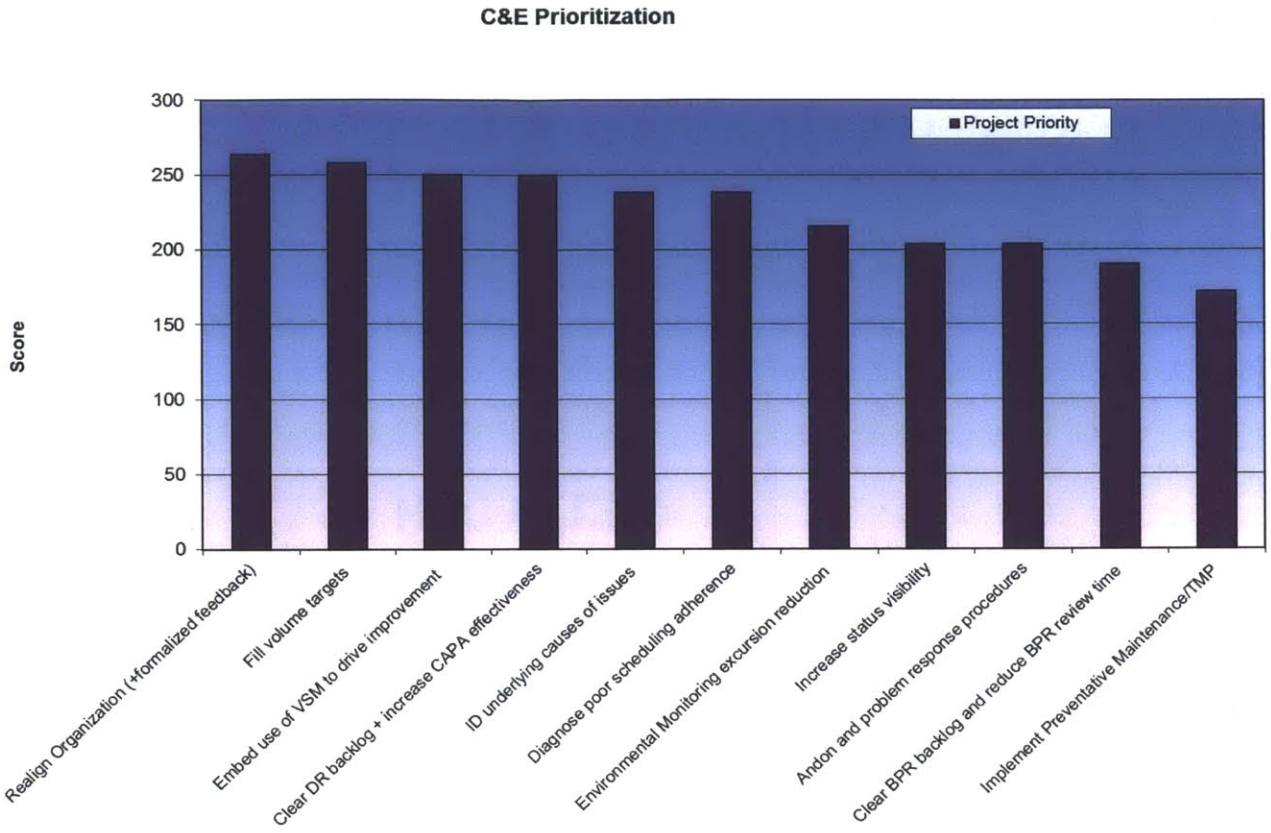


Figure 25: C&E Matrix Short Term Prioritization

From Figure 25 it is apparent that the high impact short term projects are ones that involve organizational fixes and root cause analysis whereas it will be seen below in Figure 26 that the long term solutions attack the problems that are apparent on the surface. The short horizon projects represent methods to solve many of the underlying issues that are causing issues. Based on the above figure, Novartis has implemented a comprehensive realignment and is instituting a new, exhaustive Value Stream Mapping initiative. Also in progress are DR reduction projects, increased schedule monitoring, and environmental excursions reduction projects.

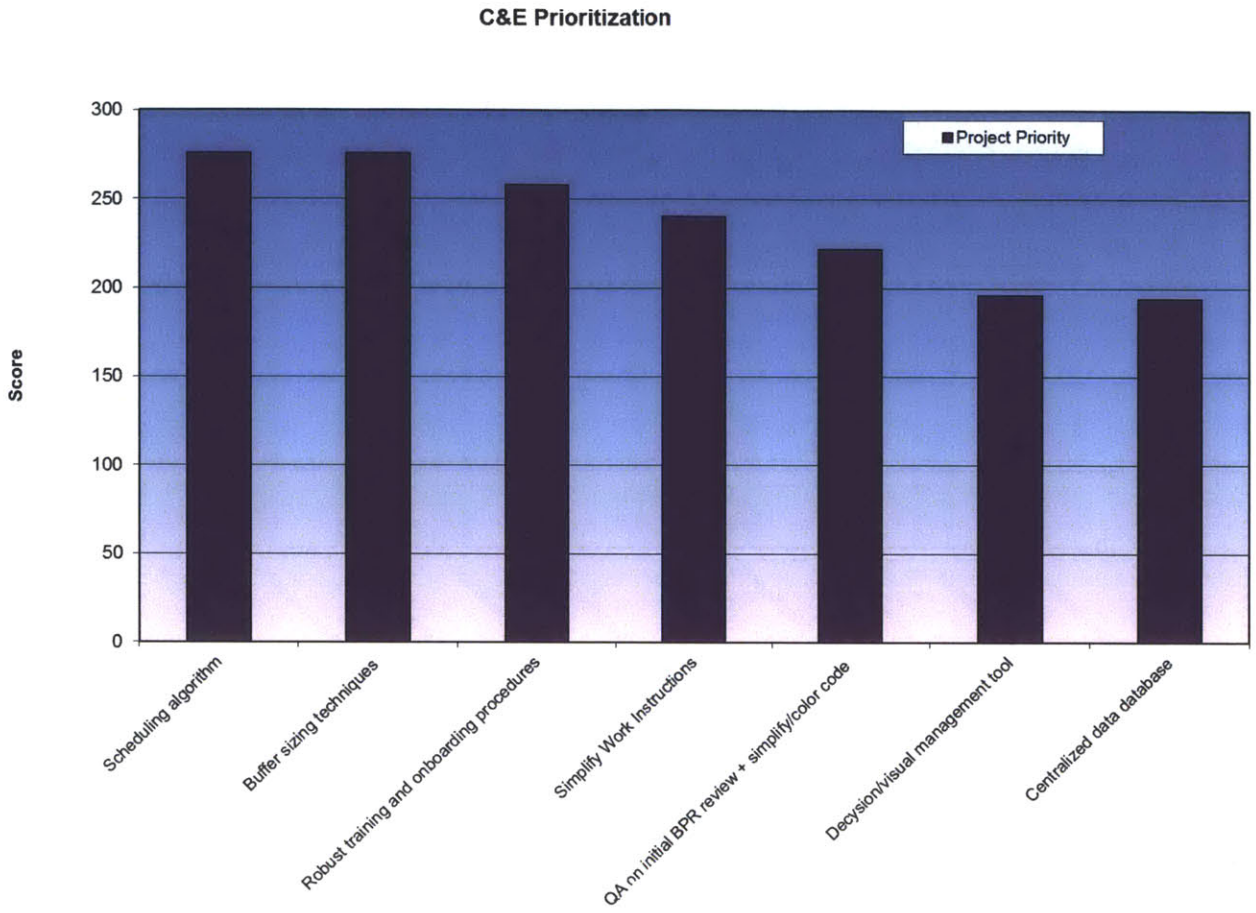


Figure 26: C&E Matrix Long Term Prioritization

The long term solutions, like those presented in Figure 26 represent ways to sustain the solutions that were created in the short term. For example, once the root cause of the scheduling issues is fully identified, an algorithm should be implemented that takes into account all issues. However, without the baseline knowledge to create relevant inputs, the computer program would be of limited value.

6 Filling Volume Target Analysis

The following section will show an analysis of a high impact short term project as determined through the value stream mapping exercise and the subsequent prioritization technique detailed above.

6.1 Filling Process Overview

The filling process is dominated by strict regulations and is a critical step in the production of a vaccine.

6.1.1 Overview of Filling Challenges

Vaccines must be filled in to vials or syringes very precisely and at very rapid rates in order to meet production goals. Since the vaccine is being administered to human patients, there is little room for variation in the amount of drug in each vial or syringe. In fact, most vaccines must be filled plus or minus 3.5% or 2% of the stated volume. Tolerances have decreased over the years as filling equipment has improved. For example, one of the flu vaccines is sold in .5ml doses meaning that, even with 3.5% tolerance, the acceptable filling range is very small: between .4825ml and .5175ml [18].

6.1.2 Motivations for Improvement

When regulations were less strict, the old method of determining a filling target was not to select a target in the center of the range, but instead something less thereby allowing the vaccine manufacturers to fill less product on average, into each vial or syringe. Over long time horizons, this amounted to large savings for the manufacturer. This was possible because the machines were very precise in comparison to the filling volume windows. However, now that tolerances have decreased and the machines have stayed largely the same, these misplaced targets are causing significant waste. The following figure shows how a typical set of specification limits looked in the past:

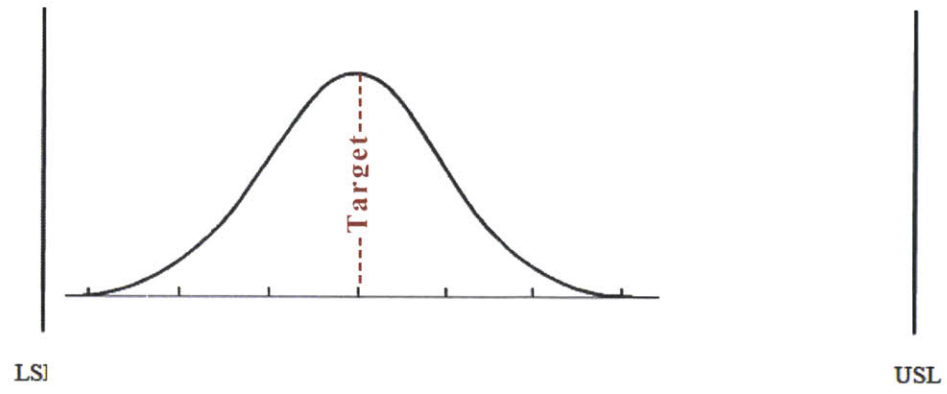


Figure 27: Past Filling Specification Limits

Where LSL means lower specification limit and USL is upper specification limit. In the situation shown in Figure 27, the filling target can be placed lower than in the center of the LSL and USL as the spread is sufficiently tight in comparison with the specification limits (in effect, high C_p). However, more modern specifications are tighter and make the spread appear as below in Figure 28 since the distribution did not get any tighter, but the specification limits have become tighter. Any shift of the target away from center (as seen in the Figure 28), will cause the distribution to be outside the tighter specification limits, thereby increasing the likelihood of product filled incorrectly.

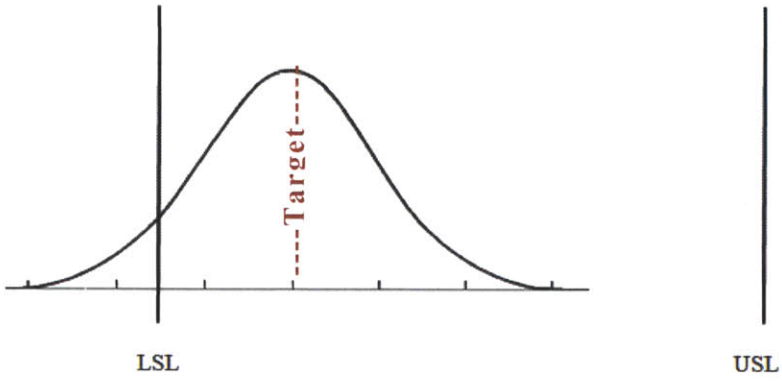


Figure 28: Modern Filling Specification Limits

All product that is filled outside of specification limits must be discarded because these limits are set in accordance with FDA and other agency guidelines. Elimination of this waste could save the company significant money as all vials and syringes that are outside the target filling range must be discarded and written off as a loss.

6.2 Capability Analysis of the Filling Lines

A comprehensive capability analysis of the filling lines at the Rosia plant was performed to determine if the any filling issues were present.

6.2.1 Capability Analysis Definitions

At a very high level, a capability analysis is performed to determine if a process is statistically able to complete the required tasked within a defined set of specifications. There are two important statistics that a frequently used in capability analyses: C_p and C_{pk}. C_p is used to determine the tightness of the cluster of data points and is calculated as seen in the below formula [19]:

$$C_p = \frac{Upper\ Specification\ Limit - Lower\ Specification\ Limit}{6\sigma}$$

Equation 3: Calculation of Cp

Using the analogy of a car parking in a garage (where the garage width is defined by the specification limits), C_p can be thought of as the width of the car. In this analogy, the car represents the width of the normal distribution. If the car (distribution) is too wide, then the car will not fit in the garage and, if the driver still tries, the sides of the car will be scraped. Conversely, a motorcycle (thin) will fit very effectively as can be seen in the below figure.

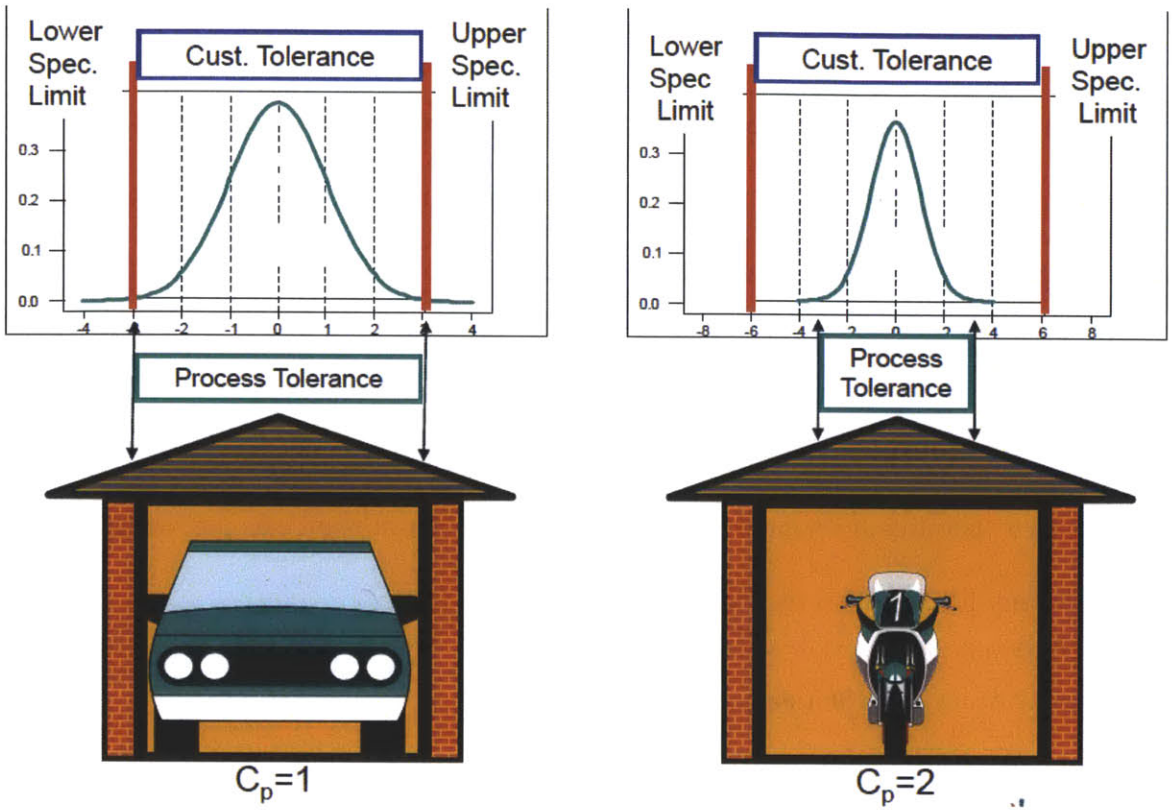


Figure 29: Illustration of the Process Capability Analogy for Cp [15]

Similarly, a distribution with a large standard deviation will not be able to fit within specification limits and the edges of the distribution will be lost to scrape (as they are outside the garage/specification limits). The location where the car is parked is defined by the C_{pk}; is the car in the center of the garage or off to the left or right? When parking the car, it is important to not only have a car that fits, but to drive it to the center of the garage or there could be an accident or it could miss the garage completely as seen below.

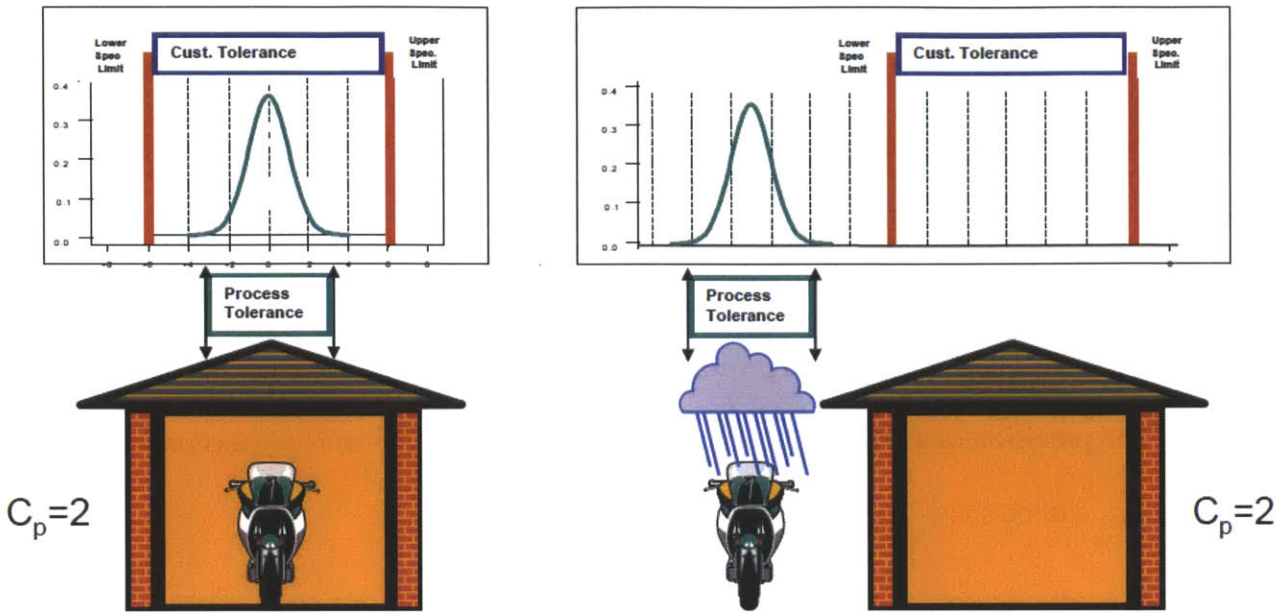


Figure 30: Illustration of the Process Capability Analogy for Cpk [15]

For the distribution, without proper targeting, even a tight distribution (high C_p) could be outside specification limits. In this way, the C_{pk} measures the accuracy and precision of the data points and is calculated as the minimum of the C_{pL} and the C_{pU} which measure how much of the spread is above or below the limits as seen in the following formulas [19] [20]:

$$C_{pU} = \frac{Upper\ Specification\ Limit - Sample\ Mean}{3\sigma}$$

Equation 4: Calculation of CpL

$$C_{pL} = \frac{Sample\ Mean - Lower\ Specification\ Limit}{3\sigma}$$

Equation 5: Calculation of CpL

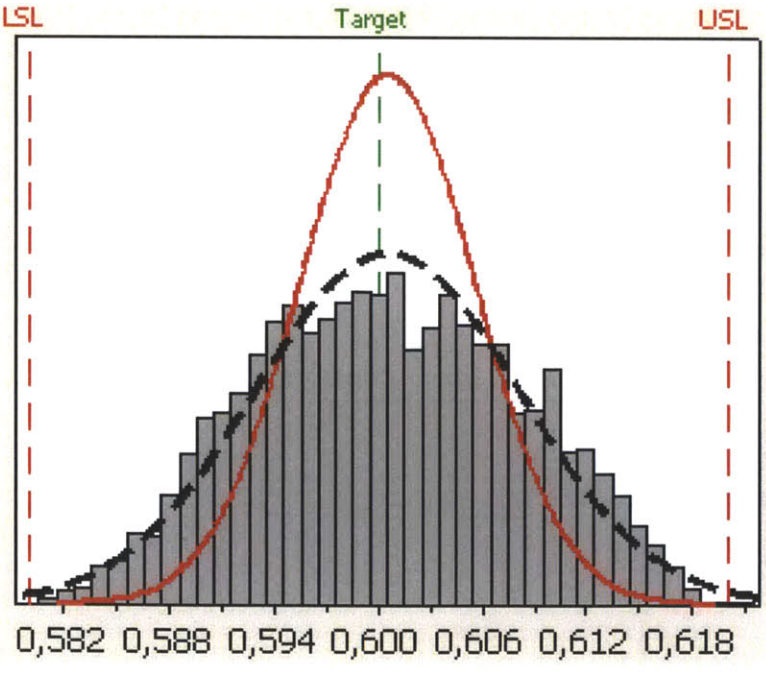
$$C_{Pk} = min(C_{pL}, C_{pU})$$

Equation 6: Calculation of Cpk

In the above formulas, σ represents the sample standard deviation. Generally, 1.33 is seen as an acceptable value of C_{pk} and C_p and anything below one indicates significant problems. With knowledge of the combination of C_{pk} and C_p, one could have a strong understanding of the expected short term performance of a process as these metrics can tell a manger the both the accuracy and precision of a process. From this knowledge, the financial repercussions can be identified (as will be show in the following section).

6.2.2 Filling Line Results

A capability analysis was performed on each of the filling lines. For the capability analysis, it was determined that the process was both in control and resembled a normal distribution as can be seen in this example graph below. For the example graph below, the C_p is 1.31 and the C_{pk} is 1.27.



[21]

Figure 31: Process Capability Graph of Flu Product [21]

While it is clear that the process has low kurtosis compared to the standard normal, it is very minimally skewed and appears to follow a bell shaped curve. After testing the assumptions, a capability analysis was performed for the major products across the four lines as can be seen below in Figure 32.

Filling Line	Product	Cp	Cpk	Cpl	Cpu	% room around target (USL-LSL)*100/Target
Line 1	Flu Product	1.31	1.27	1.34	1.27	7
	Flu Product	1.53	1.18	1.88	1.18	13
	Flu Product	1.13	1.1	1.17	1.1	4
	Flu Product	1.33	0.94	1.72	0.94	4
	Flu Product	1.57	1.55	1.6	1.55	7
	Tick Borne Encephalitis product	1.05	1.02	1.08	1.02	4
	Tick Borne Encephalitis product	1.49	1.45	1.52	1.45	7
Line 2	Tick Borne Encephalitis product	1.36	1.1	1.62	1.1	7
	Tick Borne Encephalitis product	1.28	1.03	1.52	1.03	4
	Flu product	1	0.85	1.15	0.85	4
	Flu product	1.04	0.87	1.21	0.87	4
	Flu product	1.17	1.07	1.27	1.07	7
	Haemophilus influenzae type b	1.08	0.81	1.35	0.81	4
	Flu product	0.83	0.79	0.88	0.79	4
	Flu product	1.11	1.09	1.13	1.09	7
	Tick Borne Encephalitis product	2.06	1.46	1.46	2.65	14
	Tick Borne Encephalitis product	1.84	1.7	1.99	1.7	13
Line 3	Flu product	1.41	0.86	0.86	1.96	5
	Flu product	1.53	1.38	1.38	1.68	7
	Flu product	1.22	1.07	1.37	1.07	7
	Flu product	1.25	0.77	1.73	0.77	4
Vials	Meningitis product	1.07	1.01	1.12	1.01	4
	Meningitis product	1.47	1.18	1.77	1.18	7
	Flu product	1.71	0.87	0.87	2.55	3
	Flu product	1.18	0.99	0.99	1.37	3

Figure 32: Summary Results of Capability Analysis on Filling Lines [21]

As can be seen from the above figure, there are many filling lines that are below 1.33 and are therefore not performing to expectations. Red indicates a C_{pk} or C_p that is less than 1, yellow indicates a C_{pk} or C_p that is between 1 and 1.33, and green is for all scores above 1.33 going with common technique that red indicates problems, yellow indicates that the standard is not

met, and green shows that the standard is met. By repositioning the targets, it was hypothesized, and eventually shown that significant money could be saved with relatively low risk and financial costs.

6.2.3 Financial Benefits to Repositioning Filling Target

To test the hypothesis that profit was being sacrificed because of the misplaced filling targets, a simulation was run to compare the current write-offs to those that would occur with improved filling targets. This was accomplished by simulating that the clusters of data points were centered on the center of the specification limits. Overall, it was found that over $557,000 could be saved annually by readjusting the filling targets, even when the difference in volume of filled product was taken into account. Fluvirin filled on Line 3 yielded the greatest gains. For this particular product, 10,500 parts per million are currently defective as indicated by a C_{pk} of .86. However, with target realignment, the C_{pk} would increase to 1.41 and the defect rate would decrease to 24 parts per million. Since approximately 4.4 million doses were attempted to be filled (successfully or unsuccessfully) in 2011, the number of defective doses decreased by 46,381.

It is interesting to note that the below figure shows that much of the savings is concentrated with relatively few products. In fact, approximately $400,000 (71%) in savings is able to be achieved by only focusing on the three most influential product/line combinations.

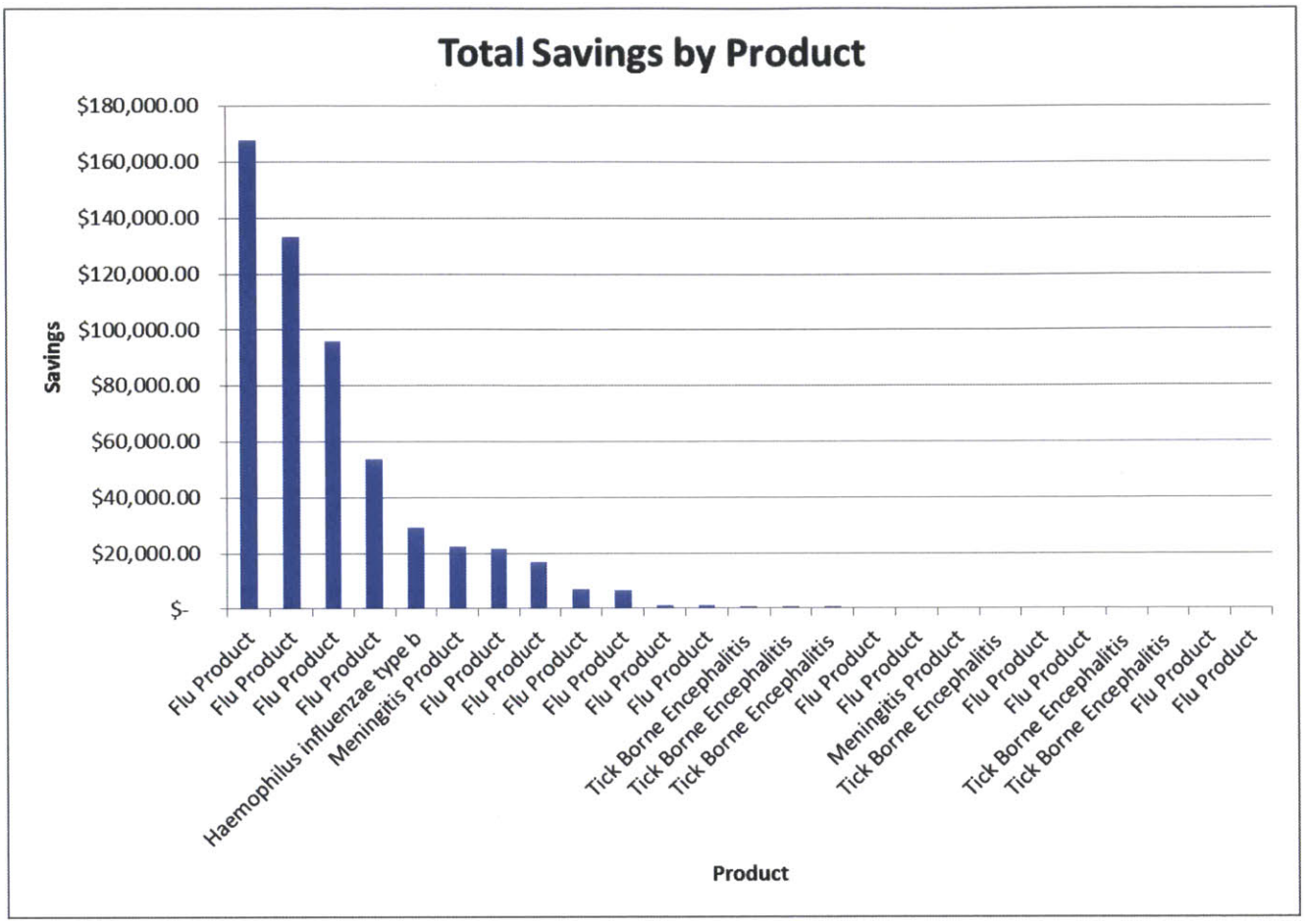


Figure 33: Expected Savings be Adjusting Filling Targets based on 2012 Simulation

The amount of impact is a function of throughput, cost of product, and prior C_p and C_{pk} values and could vary based on product selection in future years. However, it is clear that a lot of money can be saved with minimal effort by reevaluating the filling targets.

7 Conclusions and Recommendations

From the analysis performed, several important actions are recommended to improve the performance of the aseptic area in Rosia and some have already been implemented.

7.1 Strategy Implementation

It is recommended that the strategy laid out in Chapter 5 and found in Figure 25 and Figure 26 be implemented immediately to achieve more immediate results. By immediately starting the long process of changing the culture, it will allow for the foundation that allows for implementation of symptomatic fixes be built more quickly.

7.1.1 Cultural change

Many of the highly ranked short term projects deal with organizational and cultural changes. The division needs to make a significant commitment to changing the way decisions are made and how data is collected. As can be seen in Section 7.2, there are currently several projects underway. It is recommended that this continue and new projects begin. In order for this to happen, all black belt positions must be filled. Currently, while it is directed that 1% of the entire manufacturing force be dedicated to Operational Excellence as a Black Belt, this is not the case and the Black Belts are overwhelmed. This is also important to create a community of people working on Operational Excellence to provide more weight behind their recommendations.

While bolstering the Black Belt ranks will be a good place to start, there are other actions that will have positive effects as outlined in the strategy in Figure 25: C&E Matrix Short Term Prioritization and Figure 26: C&E Matrix Long Term Prioritization such as realigning the organization to have clearer accountability and reasonable scans of control, implanting value stream for all segments, and finding the root cause to many of the problems through data. These

actions will signal a cultural change that will be gut based decisions will no longer be accepted and data must be used to back up conclusions and recommendations.

Additionally, by having data readily available (through value stream maps and data collection improvement projects), data will no longer be able to be hidden on personal computers without anyone outside a specific organization able to view it. The current culture of hiding data that indicates room for improvement stifles creativity and covers up opportunities. By showing data and metric performance freely, managers will be more inclined to address the low points by implementing improvement projects.

7.1.2 Organizational then symptomatic

It will be very important to not be tempted to tackle symptomatic problems without first building a cultural and organization foundation that can support and sustain these improvements. The symptomatic problems will be high visibility and will tend to have large, measurable gains, but their results will quickly disappear if the organization is not ready for them. This can be seen with a recent LGO Batch Record Project that was initiated to increase right first time rates and decrease response times. While the results of this project were exceptional (increased right first time to above 95% and decreased review time to 2.5 days), the results have fallen off to what we see today (approximately 85% and 21 days, respectively) [22]. By building a strong foundation for these projects, the sustain phase will be easier and much more likely to become engrained in the business's fiber.

7.2 Current Projects

In accordance with the value stream mapping exercise, there are numerous projects currently under way at Novartis. Of note, two significant projects look to change the culture of the

organization: realignment and value stream mapping. The Italy sites (Siena and Rosia) are undergoing a comprehensive restructure to clarify responsibilities and accountabilities. This will serve to increase productivity as communication, personal attention, and feedback will be increased. Additionally, the Global Operational Excellence team has implemented value stream mapping for all processes with monthly review meetings and standardized metrics. This will push to increase data visibility and clarify process performance and goals.

In addition to these projects, other projects are in process to diagnose root causes (in particular, for the scheduling issues and environmental monitoring), to develop a preventative maintenance plan, and to continue with realigning the filling targets. These projects will build off the foundation of the new organizational structure and the value stream maps.

8 References

[1] D. A. Locher, "Chapter 1 - Applying Value Stream Mapping to the Development Process," in *Value Stream Mapping for Lean Development: A How-To Guide for Streamlining Time to Market* , Productivity Press, 2008.

[2] C. Sheridan, "Vaccine Market Boosters," *Nature Biotechnology,* vol. 27, no. 6, pp. 499-501, 2009.

[3] Novartis AG, "Annual Report 2012," Novartis, 2012. [Online]. Available: [4] http://www.novartis.com/downloads/investors/reports/novartis-annual-report-2012-en.pdf. [Accessed 2013 January 12].

[4] D. Gardner, Interviewee, *Global Head of Operational Excellence.* [Interview]. September 2012.

[5] M. &. H. G. Minkov, "The evolution of hofstede's doctrine," *Cross Cultural Management,* vol. 18, no. 1, pp. 18(1), 10-20, 2011.

[6] Novartis AG, "Novartis Vaccines," Novartis , 2013. [Online]. Available: http://novartisvaccines.com/. [Accessed 2013 January 10].

[7] D. Sita, "Forecasting and Planning for a Multi-Product Seasonal Production Facility," Massachusetts Institute of Technology, Cambridge, MA, 2011.

[8] Novartis Group Companies, "Vaccines and Diagnostics," Novartis, January 2012. [Online]. Available: http://www.novartisvaccines.com/downloads/5a_Vaccines_Diagnostics_EN.pdf. [Accessed 10 January 2013].

[9] K. Mitchell, "Novartis Operational Excellence," Holly Springs, NC, 2013.

[10] Novartis AG, "Worldwide Sites," Novartis, 2013. [Online]. Available: http://www.novartisvaccines.com/about-vaccines/worldwide_sites.shtml. [Accessed 10 January 2013].

[11] D. O'Hagan, "MF59 is a safe and potent vaccine adjuvant that enhances protection against influenza virus infection," *Expert Review of Vaccines,* vol. 6, no. 5, pp. 699-710, 2007.

[12] "About Menveo," Novartis , 2011. [Online]. Available: http://www.menveo.com/about/. [Accessed 25 January 2013].

[13] M. Rother and J. Shook, Learning to See : Value Stream Mapping to Create Value and Eliminate Muda, Brookline, MA: Lean Enterprise Institute, 2003.

[14] P. W. James, "Value Stream Mapping," in *Manufacuring Engineering*, 2006, pp. 145-146, 148, 150-156.

[15] O. E. Team, Writer, *IQP Green Belt Slide Presentation.* [Performance]. Novartis Vacines, 2012.

[16] T. Fugate, "The Batch Record: A Blueprint for Quality and Compliance," *Compliance Handbook for Pharmaceuticals, Medical Devices, and Biologics,* vol. 136, pp. 247-273, 2005.

[17] S. Pavlina, "How to Prioritize," StevePavlina.com, 22 May 2007. [Online]. Available: http://www.stevepavlina.com/blog/2007/05/how-to-prioritize/. [Accessed 20 February 2013].

[18] Novartis Vaccines and Diagnostics, *Agrippal 2013: Consumer Medicine Information,* Siena, IT, 2012.

[19] KnowWare International Inc., "Cp, Cpk and Process Capability Analysis," KnowWare, 2013. [Online]. Available: http://www.qimacros.com/control-chart-formulas/cp-cpk-formula/. [Accessed

24 February 2013].

[20] Production-Quality Systems, Inc., "Capability Analysis," PQ Systems, 2013. [Online]. Available: [1] http://www.pqsystems.com/qualityadvisor/DataAnalysisTools/capability_analysis.php. [Accessed 24 February 2013].

[21] R. Kumar, *Process Capability of the Aseptic Filling Lines,* Siena, Italy, 2013.

[22] R. Ford, "Using Value Stream Mapping to Improve Documentation Processes in the Briopharmacutical Industry," Massachusetts Institute of Technology, Cambridge, MA, 2010.

9 Appendix

9.1 Schedule Adherence

Scheduling Performance Since Start of 2012								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
Overall data	Overall batches planned	2145	441	92	1002	63	331	216
	Overall batches performed (SAP)	1042	205	42	531	31	84	149
	Total batches completed	1494	330	50	793	54	127	153
	Overall (SAP) %	48.58%	46.49%	45.65%	52.99%	49.21%	25.38%	68.98%
	Total %	69.75%	62.12%	84.00%	66.96%	57.41%	66.14%	97.39%
Filtration	batches planned	570	139	0	421	0	10	0
	Overall batches performed (SAP)	188	38	0	150	0	0	0
	Total batches completed	509	120	0	380	0	9	0
	% with rule +/-3gg (SAP)	32.98%	27.34%		35.63%		0.00%	
	% without rule +/-3gg	89.30%	86.33%		90.26%		90.00%	
Formulation	batches planned	439	87	21	97	18	17	199
	Overall batches performed (SAP)	310	54	13	80	15	7	141
	Total batches completed	331	64	14	79	15	12	147
	% with rule +/-3gg (SAP)	70.62%	62.07%	61.90%	82.47%	83.33%	41.18%	70.85%
	% without rule +/-3gg	75.40%	73.56%	66.67%	81.44%	83.33%	70.59%	73.87%
Filling	batches planned	532	100	31	238	21	129	13
	Overall batches performed (SAP)	233	57	14	155	0	0	7
	Total batches completed	296	71	19	167	19	16	4
	% with rule +/-3gg (SAP)	43.80%	57.00%	45.16%	65.13%	0.00%	0.00%	53.85%
	% without rule +/-3gg	55.64%	71.00%	61.29%	70.17%	90.48%	12.40%	30.77%
Inspection	batches planned	604	115	40	246	24	175	4
	Overall batches performed (SAP)	311	56	15	146	16	77	1
	Total batches completed	371	75	17	167	20	90	2
	% with rule +/-3gg (SAP)	51.49%	48.70%	37.50%	59.35%	66.67%	44.00%	25.00%
	% without rule +/-3gg	61.42%	65.22%	42.50%	67.89%	83.33%	51.43%	50.00%

9.2 Deviation Reports

DR's (by type) per 1000 batches							
	Adjuvant	Flu without MF59	Lyo	Menveo	MF59	Other	Grand Total
Formulation (total)	**168.7**	**33.2**	**187.5**	**20.8**	**105.3**	**102.7**	**99.3**
Critico	4.9	0.0	0.0	0.0	0.0	2.0	2.0
Maggiore	151.6	31.0	187.5	20.8	87.7	76.3	81.3
Minore	12.2	2.2	0.0	0.0	0.0	24.5	15.5
(blank)	0.0	0.0	0.0	0.0	17.5	0.0	0.5
Filling (total)	**462.4**	**211.0**	**3666.7**	**333.3**	**266.7**	**339.3**	**341.1**
Critico	10.8	2.7	0.0	0.0	0.0	0.0	4.3
Maggiore	427.4	197.3	3666.7	333.3	244.4	289.3	311.8
Minore	24.2	11.0	0.0	0.0	11.1	50.0	24.1
(blank)	0.0	0.0	0.0	0.0	11.1	0.0	0.9
Inspection (total)	**70.1**	**43.8**	**83.3**	**48.2**	**80.6**	**92.8**	**68.5**
Critico	0.0	0.0	6.7	0.0	0.0	4.2	1.8
Maggiore	70.1	43.8	76.7	48.2	72.6	80.2	64.9
Minore	0.0	0.0	0.0	0.0	8.1	8.4	1.8
Other (total)	**9.6**	**4.0**	**0.0**	**22.0**	**51.7**	**90.3**	**36.1**
Critico	0.0	0.0	0.0	0.0	29.5	1.3	2.1
Maggiore	8.8	4.0	0.0	11.0	7.4	68.9	26.2
Minore	0.8	0.0	0.0	11.0	14.8	18.2	7.3
(blank)	0.0	0.0	0.0	0.0	0.0	1.9	0.6
Other (QC) (total)	**21.6**	**9.6**	**34.5**	**11.0**	**110.7**	**63.0**	**37.2**
Critico	8.0	3.2	6.3	0.0	11.1	2.6	4.8
Maggiore	12.8	5.6	28.2	0.0	99.6	39.0	24.7
Minore	0.0	0.8	0.0	11.0	0.0	20.1	7.1
(blank)	0.8	0.0	0.0	0.0	0.0	1.3	0.6
Grand Total	250.0	102.3	156.7	153.8	310.0	297.6	220.4
Critico	12.8	4.0	12.5	0.0	40.6	5.8	9.3
Maggiore	224.4	93.5	144.2	131.9	239.9	223.5	182.2
Minore	12.0	4.8	0.0	22.0	22.1	65.0	27.2
(blank)	10.4	4.0	0.0	22.0	59.0	93.6	37.8

9.3 Process Efficiency

The following show a breakdown of each line's efficiency by product family.

9.3.1 Line 1

Downtime due to Maintenence stops								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	00:24:22		00:12:00	00:24:00			

Downtime between Set-up and Production (minutes per batch)								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	00:19:18		00:19:30	00:12:36			

Downtime between Production and Cleaning (minutes per batch)								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	01:12:12		01:17:30	00:39:02			

Total Unplanned Downtime Time								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	01:55:53		01:49:00	01:15:38			

Changeover time (End of Production to the end of cleaning+start of set-up to start of production)								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	04:41:55		04:46:45	04:41:21			

Cycle time (Start of set-up to the end of cleaning)								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	16:30:16		17:58:45	15:51:51			

OEE								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	60.7%		68.1%	56.4%			

Inspection Cycle Time								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	13:19:21		13:31:30	13:17:55			

Filling Time								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	11:14:35		13:12:00	10:41:53			

Inspection Utlilization								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	34.53%						

Filling Utlilization								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS1	44.84%						

9.3.2 Line 2

Downtime due to Maintenence stops									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
44.61	PFS2	00:44:36			00:46:21	00:15:00			

Downtime between Set-up and Production (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	00:05:47			00:05:46	00:06:00			

Downtime between Production and Cleaning (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	00:33:50			00:34:21	00:25:00			

Downtime between Cleaning and CIP/SIP (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	01:03:25			01:07:22	00:00:00			

Total Unplanned Downtime Time									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	02:27:37			02:33:51	00:46:00			

Changeover time (End of Production to the end of cleaning+start of set-up to start of production)									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	08:33:39			09:05:45	00:00:00			

Cycle time (Start of set-up to the end of cleaning)									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	19:24:33			19:25:46	19:04:00			

OEE									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	missing			missing	missing			

Inspection Cycle Time									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	03:59:55			04:06:00	02:53:00			

Filling Time									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	12:18:57			12:08:35	15:15:00			

Inspection Utlilization									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2								

Filling Utlilization									
		Total	Adjuvant		Flu w/ MF59	lu w/o MF5	Menveo	Lyo	Other
	PFS2	56.59%							

9.3.3 Line 3

Downtime due to Maintenence stops									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
14.88	PFS3	00:14:28				00:14:28			

Downtime between Set-up and Production (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	00:32:49				00:32:49			

Downtime between Production and Cleaning (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	01:23:49				01:23:49			

Downtime between Cleaning and CIP/SIP (minutes per batch)									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	01:21:37				01:21:37			

Total Unplanned Downtime Time									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	03:32:42				03:32:42			

Changeover time (End of Production to the end of cleaning+start of set-up to start of production)									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	10:39:44				10:39:44			

Cycle time (Start of set-up to the end of cleaning)									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	12:42:16				12:42:16			

OEE									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	28.1%				28.1%			

Inspection Cycle Time									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	11:06:51				11:06:51			

Filling Time									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	09:16:56				09:16:56			

Inspection Utlilization									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	16.43%							

Filling Utlilization									
		Total	Adjuvant		Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
	PFS3	18.36%							

9.3.4 Vials

Downtime due to Maintenence stops									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
27.00	Vial	00:30:18	00:05:00			00:48:45	00:29:48		

Downtime between Set-up and Production (minutes per batch)									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	00:39:16	00:56:30			00:54:45	00:27:22		

Downtime between Production and Cleaning (minutes per batch)									
		Total	**Adjuvant**	**Flu w/ MF59**		**lu w/o MF5**	**Menveo**	**Lyo**	**Other**
	Vial	01:05:21	01:02:15			01:19:30	00:49:27		

Total Unplanned Downtime Time									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	02:14:55	02:03:45			03:03:00	01:46:37		

Filling Time									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	12:49:57	14:51:45			11:08:15	12:42:38		

Changeover time (End of Production to the end of cleaning+start of set-up to start of production)									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	05:15:13	05:47:30			05:39:15	04:54:44		

Cycle time (Start of set-up to the end of cleaning)									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	17:48:21	20:39:15			16:47:30	13:54:05		

OEE									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	33.9%	29.3%			43.0%	32.2%		

Inspection Cycle Time									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	14:05:35	17:21:00			10:40:00	14:09:16		

Inspection Utlilization									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	22.93%							

Filling Utlilization									
		Total	Adjuvant	Flu w/ MF59		lu w/o MF5	Menveo	Lyo	Other
	Vial	22.51%							

9.4 Batch Record Review

BPR Performance Since Start of 2012								
		Total	Adjuvant	Flu w/ MF59	Flu w/o MF59	Menveo	Lyo	Other
Overall data	# of BPR's	1276	333	43	419	67	115	299
	BPR Review Time (days)	27.66	22.01	168.60	14.54	129.55	10.30	15.91
	Production: BPR Review Time (days)	23.44	17.15	164.91	10.62	128.12	5.50	11.47
	QA: BPR Review Time (days)	4.24	4.92	3.70	3.92	1.43	4.80	4.44
	With DR: BPR Review Time (days)	14.08	15.59	6.00	14.14	6.80	5.80	22.70
	# less/equal to 1 day	55	22	2	9	2	18	2
	Overall % less than 1 day	4.31%	6.61%	4.65%	2.15%	2.99%	15.65%	0.67%
	% Right First Time	85.27%	85.89%	95.35%	75.89%	97.01%	99.13%	88.29%
Filtration	# of BPR's	113	28	0	85	0	0	0
	BPR Review Time (days)	8.68	12.43	#DIV/0!	7.45	#DIV/0!	#DIV/0!	#DIV/0!
	Production: BPR Review Time (days)	6.43	8.25	#DIV/0!	5.84	#DIV/0!	#DIV/0!	#DIV/0!
	QA: BPR Review Time (days)	2.25	4.18	#DIV/0!	1.61	#DIV/0!	#DIV/0!	#DIV/0!
	With DR: BPR Review Time (days)	16.50	#DIV/0!	#DIV/0!	16.50	#DIV/0!	#DIV/0!	#DIV/0!
	# less/equal to 1 day	2	0	0	2	0	0	0
	Overall % less than 1 day	1.77%	0.00%	#DIV/0!	2.35%	#DIV/0!	#DIV/0!	#DIV/0!
	% Right First Time	97.35%	100.00%	#DIV/0!	96.47%	#DIV/0!	#DIV/0!	#DIV/0!
Formulation	# of BPR's	491	122	7	91	14	4	253
	BPR Review Time (days)	12.45	7.88	16.86	11.92	6.57	6.75	15.13
	Production: BPR Review Time (days)	9.52	5.75	9.00	8.91	4.29	5.25	11.92
	QA: BPR Review Time (days)	2.94	2.17	7.86	3.01	2.29	1.50	3.21
	With DR: BPR Review Time (days)	17.33	10.67	#DIV/0!	17.88	#DIV/0!	#DIV/0!	21.62
	# less/equal to 1 day	15	12	0	1	0	0	2
	Overall % less than 1 day	3.05%	9.84%	0.00%	1.10%	0.00%	0.00%	0.79%
	% Right First Time	94.09%	96.72%	100.00%	90.11%	100.00%	100.00%	93.68%
Filling	# of BPR's	273	83	10	119	18	1	42
	BPR Review Time (days)	14.74	16.67	13.90	13.13	5.22	7.00	19.98
	Production: BPR Review Time (days)	7.36	6.93	11.20	7.40	3.94	3.00	8.74
	QA: BPR Review Time (days)	7.38	9.75	2.70	5.72	1.28	4.00	11.24
	With DR: BPR Review Time (days)	17.61	18.90	#DIV/0!	14.33	6.00	#DIV/0!	24.71
	# less/equal to 1 day	3	1	0	1	1	0	0
	Overall % less than 1 day	1.10%	1.20%	0.00%	0.84%	5.56%	0.00%	0.00%
	% Right First Time	62.27%	61.45%	90.00%	55.46%	94.44%	100.00%	61.90%
Inspection	# of BPR's	399	100	26	124	35	110	4
	BPR Review Time (days)	60.69	46.62	268.96	22.67	242.69	10.46	22.25
	Production: BPR Review Time (days)	56.43	42.17	266.00	18.23	241.51	5.54	11.75
	QA: BPR Review Time (days)	4.25	4.44	2.96	4.44	1.17	4.93	10.50
	With DR: BPR Review Time (days)	9.02	16.70	6.00	8.86	7.33	5.80	#DIV/0!
	# less/equal to 1 day	35	9	2	5	1	18	0
	Overall % less than 1 day	8.77%	9.00%	7.69%	4.03%	2.86%	16.36%	0.00%
	% Right First Time	86.72%	89.00%	96.15%	70.97%	97.14%	99.09%	25.00%

9.5 Short Term Cause and Effect Matrix

Author: Zach Wolf
Date: 18-01-12
Revision: 0

Novartis Project Selection Cause and Effect Matrix

			9	6	4	7	7	4	9	
			1	2	3	4	5	6	7	
	Project Name	**Function**	Criticality	Resource Availability	Project Compatibility	Economic Feasibility	Vulnerability	Accessibility	Effects	Total
1	Realign Organization (+formalized feedback)	Organizational	1	3	9	9	3	9	9	264
2	Fill volume targets	Process	9	3	3	9	9	3	1	258
3	Embed use of VSM to drive improvement	Organizational	1	3	9	9	1	9	9	250
4	Clear DR backlog + increase CAPA effectiveness	Organizational	1	3	9	9	1	9	9	250
5	ID underlying causes of issues	Organizational	1	1	9	9	1	9	9	238
6	Diagnose poor scheduling adherence	Scheduling	1	1	9	9	1	9	9	238
7	Environmental Monitoring excursion reduction	Process	9	3	3	3	3	9	3	216
8	Increase status visibility	Organizational	3	1	9	3	3	3	9	204
9	Andon and problem response procedures	Organizational	3	1	9	3	3	3	9	204
11	Clear BPR backlog and reduce BPR review time	Organizational	3	1	9	3	1	3	9	190
12	Implement Preventative Maintenance/TMP	Process	3	3	9	3	1	9	3	172
13	Continue with DR Reduction Project	Process	3	3	3	3	9	1	3	172

9.6 Long Term Cause and Effect Matrix

Author: Zach Wolf
Date: 18-01-12
Revision:

Novartis Project Selection Cause and Effect Matrix

			7	2	6	7	7	3	9	
			1	2	3	4	5	6	7	
	Project Name	**Function**	Criticality	Resource Availability	Project Compatibility	Economic Feasibility	Vulnerability	Accessibility	Effects	Total
1	Scheduling algorithm	Scheduling	9	1	3	3	9	3	9	257
2	Buffer sizing techniques	Scheduling	9	1	3	3	9	3	9	257
3	Robust training and onboarding procedures	Organizational	3	3	9	9	3	3	9	255
4	Simplify Work Instructions	Process	1	3	9	9	3	3	9	241
5	QA on initial BPR review + simplify/color code	Organizational	3	3	3	9	9	3	3	207
6	Decysion/visual management tool	Process	3	1	9	3	3	1	9	203
8	Centralized data database	Process	3	3	9	1	3	1	9	193
										0

\