# Lean Transformation Methodology and Implementation in Biopharmaceutical Operations

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

Master of Business Administration
and
Master of Science in Chemical Engineering

In Conjunction with the Leaders for Manufacturing Program at the Massachusetts Institute of Technology
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## ABSTRACT

Amgen's Operations division is responsible for the production, release and distribution of commercial and clinical products. Due to industry consolidation, impending competition and revenue impacts, Amgen is facing the need to rapidly improve the Operations division and align different manufacturing sites. In order to achieve these goals, the Operations Improvement group is leading an initiative to bring about a lean transformation of Amgen's operations.

This thesis analyzes the initial operational excellence efforts underway within Amgen Operations. The analysis includes an overview of the process by which the continuous improvement methodology and strategy were constructed, the creation of a training curriculum and the initial implementation of the continuous improvement methodology at specific manufacturing sites. In addition, the thesis explores the environment in which this program operates and the cultural and business drivers that support and detract from the efforts.

The following conclusions were developed as a result of the analysis of the lean transformation efforts at Amgen. First, company and industry specific nomenclature is essential to make lean principles contextually relevant for the biopharmaceutical industry. Additionally, relevant metrics are needed to facilitate multi-site alignment and drive the desired behavior. Finally, continuous improvement efforts can effectively leverage a science-based culture by applying it to a new business context.

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*Finally, and most importantly, he would like to express his gratitude to his wife Amber for her unending patience and support over the years and to his parents for their wisdom and guidance.*

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## Note on Proprietary Information

In order to protect proprietary Amgen information, the data presented throughout this thesis have been altered and do not represent the actual values used by Amgen, Inc. The process steps, operational efficiencies, cycle times and dollar values have been disguised in order to protect competitive information where necessary.

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# 1. Introduction

## *1.1. Project Context and Drivers*

Amgen is a leading biotechnology company and has helped to pioneer the development and production of recombinant protein therapeutics throughout their twenty-eight year history. Most of Amgen's success was born from their first product, Epogen, which established a new standard of care for anemia and created the company's core Erythropoiesis-Stimulating Agents (ESA) business. Amgen's product portfolio was expanded to include Neupogen for neutropenia, as well as the next generation products Aranesp and Neulasta.[1,2] Parallel with the successes of these products, Amgen was busy expanding their product pipeline and manufacturing capabilities through internal development and acquisitions of other biotechnology companies. The speed of this expansion helped to secure Amgen's standing in the industry, but also led to disparate business and manufacturing practices among the different manufacturing sites. As the company matures, these differences have become more apparent and the need for alignment and improvement has become a focus for the company. In addition, Amgen is now facing additional challenges including industry consolidation, impending competition from follow-on biologics and potentially significant revenue impact on Amgen's core Erythropoiesis-Stimulating Agents (ESA) business due to both safety concerns and changes in Medicare reimbursement guidelines.

Today within Amgen, the Operations division is responsible for the production, release and distribution of Amgen's commercial and clinical products. This division operates under the aspiration to serve every patient, every time, an aspiration that has always been fulfilled throughout the company's history. The continued fulfillment of this aspiration still drives operations, even in the face of the many recent challenges. To address these issues, the company is currently undergoing reorganization and rationalization efforts, including staff reductions of 12-14%, delays in new capital projects and the closing of a manufacturing plant. In parallel with these activities, a small team within Operations, the Operations Improvement group, was tasked with leading an initiative to bring about the lean transformation of Amgen's operations. While

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[1] (About Amgen - Company History, 2008)

[2] (Amgen – Patients – Products, 2008)

the specific mechanisms and requirements of this initiative were not fully specified at the project's outset, the end goal was clear: improve the operations network's overall productivity and efficiency to be an asset for Amgen when facing future challenges.

## 1.2. Problem Statement

In order to fulfill the needs of the company, the Operations Improvement group needs to create a cohesive, sustainable approach to continuous improvement within Amgen. As discussed, several factors are driving the Operations division towards a lean transformation, all of which are intended to be addressed through the group's efforts. To achieve this, the group wants to 1) implement a common continuous improvement methodology, 2) standardize common practices across the network, 3) achieve sustainable and measurable operational or financial results, and 4) foster a culture that combines both compliance and continuous improvement.

The drivers faced by Amgen and the approach taken to address them are very similar to those faced by myriad other companies, both in the biotechnology industry and beyond. However, unlike other companies, this initiative seeks to make use of Amgen's science based culture to implement and sustain the broad adoption of a science based approach to managing both business and production processes. This thesis claims, based on observations during the development and initial roll-out of the Amgen continuous improvement program, that Amgen's core value of *being science-based* will allow the company to embrace and sustain lean manufacturing ideas and principles throughout their operations.

The aim for this thesis is to analyze the initial operational excellence efforts underway within Amgen Operations. The analysis includes an overview of the process by which the continuous improvement methodology and strategy were constructed, the creation of a training curriculum and the initial implementation of the continuous improvement methodology at specific manufacturing sites. In addition, the thesis explores the environment in which this program operates and the cultural and business drivers that support and detract from the efforts.

## 1.3. Thesis Overview

This document is organized as described below:

**Chapter 1** outlines the general motivation for this project and gives an overview of the thesis.

**Chapter 2** provides a brief discussion of Amgen's history and products. It also highlights some of the recent challenges that Amgen faced during the project that help to frame the context for the project.

**Chapter 3** introduces the project setting and goals along with the approach that was taken.

**Chapter 4** examines the development of the process excellence methodology at Amgen, including both the specific tools included and the associated biotechnology-specific training materials that were developed for use throughout Amgen. It also introduces two in-house tools that were developed as part of the project that help to highlight potential improvement projects.

**Chapter 5** discusses the activities involved in the initial roll-out of the process excellence methodology at two of Amgen's commercial manufacturing sites.

**Chapter 6** reviews the changes in Amgen's organizational structure and the effects of these changes on the process excellence project. In addition, the behaviors and metrics affecting decisions at the company are discussed along with potential improvement areas.

**Chapter 7** evaluates the initial progress of the lean transformation process and summarizes the findings from the project.

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# 2. Amgen Company Background

## *2.1. Amgen Organization, Products and Early Success*

Amgen (originally AMGen – Applied Molecular Genetics) was incorporated in 1980 to pioneer 'the development of novel and innovative products based on advances in recombinant DNA and molecular biology."[3] From this initial start, the company quickly focused its business on developing recombinant protein therapeutics. Amgen's first drug, EPOGEN® (Epoetin alfa), was the first biopharmaceutical industry blockbuster. Even more impressive than this first victory, Amgen's second drug NEUPOGEN® (Filgrastim) arrived as the industry's second blockbuster drug in quick succession.[4]

The company continued to build upon its early successes, investing heavily into research and development to discover new therapeutics and into manufacturing capacity to meet the demands for its products. Figure 1 depicts the locations of Amgen Operations facilities, including manufacturing, distribution and research and development.

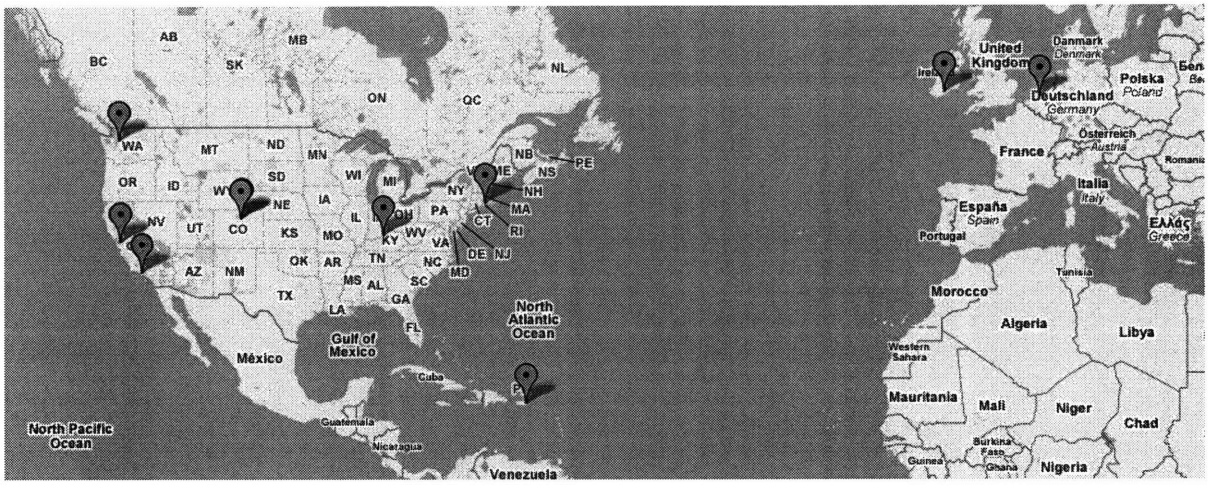


**Figure 1: Amgen Operations Locations**

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[3] (About Amgen - Company History, 2008)

[4] (About Amgen - Company History, 2008)

In addition to the success of their products, Amgen's achievements in the biopharmaceutical industry can be traced to their science-based culture and their continued commitment to *being science-based*, which is listed first among the company's values. Amgen defines being science-based as follows:

> Our success depends on superior scientific innovation, integrity and continuous improvement in all aspects of our business through the application of the scientific method. We see the scientific method as a multi-step process that includes designing the right experiment, collecting and analyzing data and rational decision making. It is not subjective or emotional, but rather a logical, open and rational process. Applying the scientific method in all parts of the organization is expected and highly valued.[5]

[5] (About Amgen – Mission & Values, 2008)

## 2.2. Amgen Company Growth

The success of Amgen's initial entrants into the biopharmaceutical market helped sustain the company's remarkable growth through the 21st century. Amgen's revenues, shown in Figure 2 below, rapidly grew to over $14 billion by 2006. To sustain their growth, Amgen continued to fund internal research and development while also strategically acquiring new products through licensing agreements and merger activities.

Amgen has acquired several companies over the years to increase its product portfolio and develop the scope of research activities. In 2002, Amgen announced the acquisition of Immunex Corporation for $16 billion in cash. The acquisition allowed Amgen to gain rights in North America for the rheumatoid arthritis treatment Enbrel.[6] More recently, Amgen acquired Abgenix, Inc. and its cancer drug Vectibix.[7] These two specific acquisitions (as well as some others not mentioned here) resulted in Amgen inheriting manufacturing facilities and production staff in addition to the drugs in development.

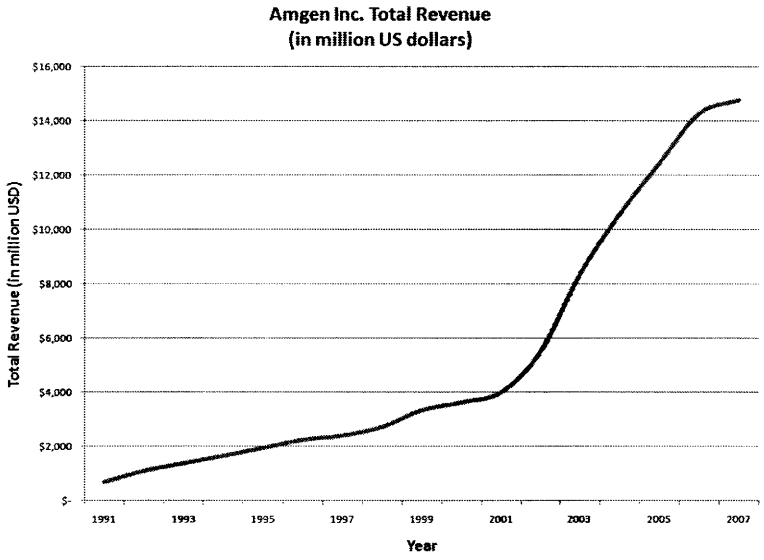


**Figure 2: Amgen Revenue Growth 1991 – 2007**[8]

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[6] (TheStreet.com Staff, 2001)

[7] (About Amgen - Company History - Acquisitions, 2008)

[8] Created by the author from Amgen, Inc. financial statements

## 2.3. Recent Challenges

Recently, Amgen's position at the top of the biopharmaceutical industry has been challenged due to regulatory setbacks, pressure on sales and new sources of competition. The primary drivers of these challenges were the recent actions by the Food and Drug Administration (FDA) and the federal Medicare and Medicaid programs. In 2007, the federal government reduced the maximum reimbursements for Aranesp by Medicare and Medicaid. In addition, the FDA recommended "lower dosages of the class of anemia drugs that includes Aranesp and another Amgen product, Epogen, after trials raised safety questions. Those two drugs account for about half of Amgen's sales and more than half of profits."[9] The safety concerns are still being debated among scientists and doctors, however the impacts on sales from the ESA business are substantial. The FDA has already directed Amgen to include a black box warning on Epogen and Aranesp packages, "the highest level of warning contained in drug information provided to doctors and patients."[10]

Amgen is also facing potential direct competition for its products for the first time in its history. The Swiss pharmaceutical company Roche attempted to break into the market with Mircera, a direct competitor to Epogen and Aranesp. Amgen responded to Roche's attempted entry into the U.S. market with a patent-infringement lawsuit which it subsequently won.[11,12] In addition to the efforts of Roche, Novartis, another Swiss pharmaceutical company, has successfully launched a generic version of Epogen in Europe where Amgen no longer has remaining patent protection.[13] Efforts are still underway to bring the Novartis product to the United States.

In response to revenue pressures, Amgen announced a reduction in force of 12 – 14% and a restriction on capital expenditures in August 2007.[14]

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[9] (Aenlle, 2007)

[10] (U.S. to Review Anemia Drugs for Safety, 2007)

[11] (Amgen Defends Its Turf as Competition Looms for Anemia Drug, 2007)

[12] (Amgen Wins Patent Battle Over Roche's Anemia Drug, 2007)

[13] (Generic Anemia Drug Allowed, 2007)

[14] (Chang, 2007)

# 3. Project Scope and Approach

## 3.1. Project Setting

The activities and research for this thesis occurred with the Operations Improvement (formerly Corporate Manufacturing) group at Amgen's corporate headquarters in Thousand Oaks, CA. The group was initially created to facilitate projects that affected all manufacturing sites, and was recently tasked with the development and deployment of a continuous improvement methodology and program for use throughout all of Amgen Operations. The group has focused its initial efforts in the program on the operations directly involved with manufacturing of products at the individual manufacturing sites and will later move on to the remainder of the division. The ultimate purpose of the continuous improvement program is to mature practices throughout all operations to preserve the company's competitive position in the industry and position it for the future.

## 3.2. Goals for Internship

The primary goal of this internship and subsequent thesis was to participate fully in the development, strategy and initial roll-out of Amgen's continuous improvement program as both an insider within the Operations Improvement group and an outsider with prior industry experience and access to academic research on successful implementation of continuous improvement efforts at other firms. While working within this main objective, the internship also sought to determine what processes, metrics and/or governance needed revision or creation to help facilitate the group's improvement efforts. This combination of goals, along with delivery of tangible benefits to the manufacturing sites, hoped to ensure both the initial success and long-term sustainability of Amgen's lean transformation efforts.

## 3.3. Approach

To achieve the goals of the internship, the project was divided into two main work streams, each with their own deliverables. These work streams had a large degree of connectivity,

however it was useful to segregate them to measure progress on both the development and execution of the lean transformation effort.

The first work stream was termed *Continuous Improvement Program Development.* This segment of activities encompassed working with Amgen employees and experts on the creation of the deployment strategy for continuous improvement at Amgen. Additionally it involved assisting with the development of the continuous improvement methodology and the selection of specific lean and process improvement tools to be utilized as part of the program, including the creation of "in-house" tools specifically tailored to Amgen operations.

The second work stream was dubbed *Initial Roll-Out to Manufacturing Sites* and entailed two separate roll-out efforts to different Amgen locations to both educate site-based operations and exercise the newly created methodology and tools. This iterative process fed back into the program development work stream as the methodology and tools were either validated or discovered to not fully support the efforts. Ultimately, this work stream also served to deliver quantifiable value and tangible results to the sites (e.g. cost savings or cycle time reduction) in order to build momentum for the program throughout Amgen.

# 4. Lean Transformation Methodology Development

## *4.1. Background on Lean Transformations*

In order to fully understand the inherent challenges in developing a lean transformation methodology within Amgen, it is necessary to first discuss the core principles and tools of lean, the current state of operational excellence practice in the biopharmaceutical industry and the challenges inherent to these industries that limit continuous improvement.

### 4.1.1. Brief Introduction to Lean Principles and Basic Tools

Through the book *The Machine That Changed the World,* the world was formally introduced to the principles of lean manufacturing,[15] a term coined by the authors. The basic concepts involved in lean manufacturing were described as a company-wide focus on continuous improvement through the elimination of waste. This focus on eliminating waste is echoed by Taiichi Ohno, the inventor of the Toyota Production System. He categorized the different types of waste inherent in manufacturing (and work in general) as follows:

1. Waste of overproduction
2. Waste of time on hand (waiting)
3. Waste in transportation
4. Waste of processing itself
5. Waste of stock on hand (inventory)
6. Waste of movement
7. Waste of making defective products[16]

The elimination of these wastes represented the core ideals of lean manufacturing, from which all other concepts and practices were driven. Many companies attempted to mimic the Toyota approach, but were unable to replicate their results even when focused on eliminating waste.

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[15] (Womack, Jones, & Roos, The Machine That Changed the World, 1990)

[16] (Ohno, 1988)

Given that Toyota was very open in allowing other companies to learn about and observe their way of operating, why was it so difficult to replicate? Indeed, companies attempting lean transformations were able to copy the tools and methods used by Toyota, but were unable to sustain the results.

The answer seems to lie in the underlying principles of the Toyota Production System. While the focus on waste, reliance on teamwork and use of simple yet effective tools are very important in lean, they are not sufficient for success. Rather, the company needs to have an underlying foundation and reliance upon basic scientific principles in order to drive improvements through lean manufacturing. This theory on the core foundations of lean manufacturing was proposed by Spear and Bowen, who observed that "the rigid specification [of the Toyota Production System] is the very thing that makes the flexibility and the creativity possible."[17] Due to their reliance on the scientific method for continuous improvement activities, "Toyota Production System [and thus true lean manufacturing] creates a community of scientists."[18] In accordance with this theory, a lean transformation at any company should begin first with a focus on applying the scientific method to the way they conduct business. Further, the application of 'typical' lean tools and methods should occur in accordance with the following proposed rules:

Rule 1 – All work shall be highly specified as to content, sequence, timing, and outcome.
Rule 2 – Every customer-supplier connection must be direct, and there must be an unambiguous yes-or-no way to send requests and receive responses.
Rule 3 – The pathway for every product and service must be simple and direct.
Rule 4 – Any improvement must be made in accordance with the scientific method, under the guidance of a teacher, at the lowest possible level of the organization.[19]

Even with vast information about the theories associated with lean principles, there are still many questions to be answered about how teams and managers should go about introducing and managing lean within an organization. In essence, how does one put these theories and concepts

[17] (Spear & Bowen, 1999)

[18] (Spear & Bowen, 1999)

[19] (Spear & Bowen, 1999)

into practice to help achieve sustainable success? There is no clear answer to this issue and in many ways the ultimate success of any lean transformation is governed by the commitment of the organization to a lasting and complete change in operations. However, further research on the underlying principles at Toyota has given rise to the following lessons for any manager or leader of improvement activities within a company.

Lesson 1 – There's no substitute for direct observation.
Lesson 2 – Proposed changes should always be structured as experiments.
Lesson 3 – Workers and managers should experiment as frequently as possible.
Lesson 4 – Managers should coach, not fix.[20]

The core principles outlined above, specifically the reliance on the scientific method at all levels of the organization to drive improvement, are the true essence of lean manufacturing. There are literally dozens of books and guides to help companies with the basic tools and practices involved with lean manufacturing, but these alone are not sufficient to drive sustainable lean efforts. It is the author's belief that a true lean transformation is only possible when there is 1) a company-wide focus on improvement, 2) a reliance on scientific principles and 3) a trained and empowered workforce able to drive improvement activities.

### 4.1.2. Overview of Lean in the Biopharmaceutical Industry

Lean transformation efforts, or other continuous improvement programs, are fairly common in established industries. Companies within younger industries, such as the biopharmaceutical industry, have been slower to adopt these practices mainly due to their focus on establishing themselves in the initial market. As the industry matures, an increased focus on continuous improvement is being observed at many companies. The same can be said for traditional pharmaceutical companies as the combined industries face increased regulatory and cost pressures.

Several surveys have been conducted to assess the current state of the biopharmaceutical industry with respect to continuous improvement programs. One specific survey was the 2003

[20] (Spear S. J., 2004)

BioBenchmark[SM] study conducted by Tefen, an international management consulting firm, and BioPharm International.[21] At the time of this survey, the biopharmaceutical industry was just beginning to focus on operational excellence programs to sustain competitive advantage, as is evidenced by the fact that 84% of the companies surveyed did not have systems in place to drive improvement activities.[22]

Even as more biopharmaceutical manufacturers talk about implementing process improvement programs like lean, there is a general perception that lean will not work in the industry. With the successes of lean principles elsewhere, "[c]an an industry that spends so much money each year working on 'undevelopable' compounds and that has one of the highest waste and rework levels, and the highest cycle times, on its manufacturing side, afford to ignore these concepts?"[23] Several reasons are given for this incompatibility, from the complexity of the processes to the strong regulatory pressures governing the processes. The simple truth, however, is that many opportunities for improvements exist within these regulated manufacturing facilities that do not affect the process steps themselves or the regulated steps. Given that most of the cycle time associated with the production of a biopharmaceutical protein is waiting time (waiting for cleaning, set-up, testing, release, etc.), vast improvements in throughput are possible without modifying any of the filed processes or affecting GMP (Good Manufacturing Practices) requirements.

The key to applying lean principles and tools to the biopharmaceutical industry lies in the minor modification of Toyota's tools to the specific manufacturing environment. Most operations involved in the production of a protein therapeutic do not resemble the assembly line of a car plant, so in order to succeed with these concepts involves choosing tool(s) and adapting them to fit the need. Many successful improvement efforts begin with value stream mapping and simple organizational tools before moving on to more complex problem solving and analytical systems.[24]

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[21] (BioBenchmarkSM Study Team, 2003)

[22] (BioBenchmarkSM Study Team, 2003)

[23] (Shanley, 2006)

[24] (Shanley, 2006)

### 4.1.3. Obstacles to Lean Implementation in the Biopharmaceutical Industry

Major obstacles exist in any organization or industry that prevent the adoption of continuous improvement systems, from employee resistance to a lack of operational focus. There are additional obstacles in the biopharmaceutical industry that can make a lean transformation even more difficult and must be managed effectively.

First, as has been mentioned previously, the industry is highly regulated by government authorities worldwide to ensure safety for consumers of the drugs created. Recently, the United States Food and Drug Administration (FDA) has sought to address this apparent regulation obstacle to improvement as well as the total risks inherent to pharmaceutical manufacturing through the development of the Process Analytical Technology (PAT) initiative.[25] While this initiative does have continuous improvement and high-quality production in mind, it is early in its implementation and many companies are waiting to see how the regulators will evaluate its use.

Secondly, the manufacturing facilities used to produce many biopharmaceutical products were usually designed for one specific product and are therefore fairly inflexible. This inflexibility can be confounded further by the use of automation in processing, as any changes to automation procedures requires validation activities to comply with GMP requirements. As a result, the rigidity of these facilities and their control systems can serve to deter improvement efforts, as employees are unable to execute potential improvements in a timely manner, if at all.

Next, the manufacturing processes themselves are, to some degree, inherently unpredictable. The upstream process (either cell culture of fermentation) utilizes living organisms to produce the desired protein, and can vary in unpredictable ways. Despite the efforts of scientists and engineers, the variations from these upstream processes cannot be entirely eliminated, which can shift the focus from improvement in operations to fire-fighting unknown issues. This upstream variation can also have similar effects on the purification processes, as different levels of by-products or contaminants can sometimes be introduced.

Additionally, many biopharmaceutical manufacturing steps or processes are executed using a batch or semi-batch approach, rather than continuous manufacturing. This batch approach may be employed due to the nature of the developed process, for example if the designed

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[25] (FDA Office of Pharmaceutical Science, 2008)

bioreactor/fermentor reactions produce harvests collected on a set schedule rather than being collected continuously using a perfusion process. The batch approach can also be employed to hedge against potential manufacturing risks, such as the possibility of contamination or loss due to machine or human error in processing. By operating each processing step in a batch approach, firms are able to segregate any potential issues to a single batch of product, which may minimize the total product loss that could result. While it is possible that manufacturing firms could modify some of their processes to run in a more continuous approach, the large costs and uncertainty associated with modifying an existing process deter most large-scale changes post regulatory approval.

Finally, the extremely long cycle times and lead times, large inventories, complicated supply chains, requirements to always meet patient safety requirements and overwhelming quality inspection burden all serve to distract workers from continuous improvement activities.[26]

[26] (Vilalta & Hamed, 2007)

## 4.2. *Amgen Process Excellence (APEX) Methodology*

The Operations Improvement team, comprised of several Amgen employees and the author, began its process improvement efforts through the development of an Amgen themed approach to lean principles and continuous improvement. Based upon the collective experiences of the team, it was felt that the use of an Amgen-specific methodology and toolset would help to ensure adoption and long term success of the efforts. To complete the development of the approach, the team sought to explicitly incorporate the scientific method into the process excellence process while not relying on pre-configured solutions from other industries.

### 4.2.1. Review of Methodology Development Process

The early development of the Amgen Process Excellence (APEX) methodology was initially managed entirely by the Operations Improvement team. These first steps in the definition of what APEX would become were centered on both the experiences of the team members and of stakeholders involved in previous process improvement efforts within Amgen and elsewhere in the industry. The main purpose of these early discussions was to reflect on the lessons learned from previous efforts and to determine what would be most successful for the APEX initiative and what should be avoided based on previous efforts within Amgen that were unsuccessful or unpopular in the past. Amgen had attempted to deploy Six Sigma techniques in the recent past and was unsuccessful in gaining widespread acceptance. While the Quality organization had found value in the approach for its testing practices, the rest of the Operations division did not adopt Six Sigma as it was seen as an additional layer of bureaucracy due to the large training involved and project management required. Additionally, previous efforts to implement specific lean tools were hampered within Amgen because the examples used to teach the tools did not clearly align with the manufacturing processes in the company.

From these interviews and meetings, the Operations Improvement team was able to assemble an initial proposal of what the APEX methodology would entail. APEX would employ the basic principles and tools of lean and other process improvement programs but would not apply the labels associated with those concepts. This would allow the APEX approach to differentiate

itself from previous efforts within Amgen that were unsuccessful or unpopular in the past while still embracing the need for continuous improvement in the operations of the company.

Following the creation of the initial proposal, the draft methodology was distributed to 'thought leaders' throughout Amgen, at both the corporate headquarters and at many of the manufacturing sites. These different stakeholders were then asked to come to a two-day workshop at Amgen headquarters to help discuss the original APEX proposal and modify or adapt it as necessary. The end result of this workshop was a revised and agreed-upon APEX methodology with input from stakeholders throughout Operations. This revised methodology was then utilized for the initial roll-out of APEX to the manufacturing sites.

### 4.2.2. General Overview of Methodology

The APEX methodology generated through the efforts of the Operations Improvement team and the workshop participants is shown in Figure 3. The APEX process shows six distinct steps that should be followed for any process improvement project with corresponding recommended tools and deliverables for management.

The first step in the APEX approach is 'Initiate.' The activities in this step, while extremely simple, are often omitted in the typical execution of improvement projects. Through the inclusion of this step, the APEX approach ensures that everyone is properly trained and that management is fully aware of and agrees to the scope of the improvement project.

Next in the APEX methodology is the 'Baseline Current Process' step. At this stage, the team observes the process and talks with the subject matter experts to identify the specific targets to be pursued. The team utilizes tools such as value stream and/or process maps to help fully understand the problem and defines what success would look like at the end of their efforts.

Following the completion of the baseline activities, the team moves on to the 'Design Future State' stage. This is where the team employs many of the tools covered in their training curriculum (see 4.3) and ultimately generates a list of potential improvement projects. These projects are then presented by the team to the management team for prioritization and endorsement in the 'Scope, Prioritize & Agree' stage.

At this point in the process, the team is set to 'Implement' their improvement projects. As the projects are executed, the team must ensure that their goals are being met. If necessary, the team can return to earlier stages to revise and redirect their efforts under the guidance of

management. Following the completion of the improvement projects, the team documents the results of their efforts to facilitate knowledge sharing among groups and sites as part of the 'Closeout' stage.

The overall process is reminiscent of both the Deming (PDCA) Cycle – Plan, Do, Check, Act[27] and the Six Sigma DMAIC process – Define, Measure, Analyze, Improve, Control.[28] This is not a coincidence, as those well-known processes have been successfully employed for decades. The creation of an Amgen-specific process only serves to differentiate APEX from previous efforts and signify that it has been created for use at Amgen. The specific outputs and phases of the process also help management to drive the APEX efforts within their sites. By having these specific deliverables at each stage of the process, project management tools and resources can be employed to monitor and direct the improvement projects. Eventually, it is hoped that these steps and outputs will become routine and will not require large amounts of project management resources.

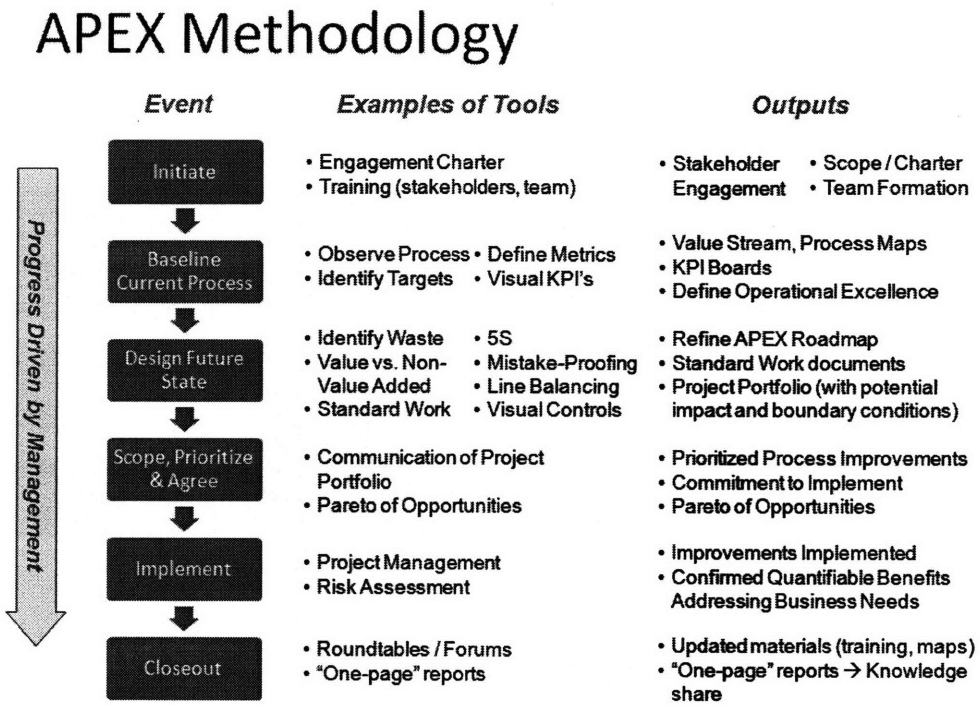


**Figure 3: Amgen Process Excellence (APEX) Methodology**

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[27] (Womack & Jones, Lean Thinking, 2003)

[28] (Motorola University: What is Six Sigma?)

In addition to the creation of the APEX methodology for use in process improvements, the Operations Improvement group also generated a maturity map to help explain the lean transformation to upper management. These stages of transformation, depicted in Figure 4, provide the concepts employed and the outputs generated at each stage.[29] The initial stage of Stability is a foundational step in the roll-out of APEX to the sites and will help management to understand the current capabilities and performance of their network. Next is Flow, which represents the state of operations once all sites have begun employing APEX to execute process improvement projects. These first two stages are hoped to be completed within 1 – 2 years after the introduction of the APEX methodology. Following the completion of the first two stages, the company will then proceed to the Pull stage where the interdependencies between all processes within a site are known and addressed. This will result in the implementation of pull processing throughout the site and ultimately throughout all of Amgen's operations. Finally, once Pull has been established, Amgen can then turn its focus outward to its suppliers and customers to optimize and improve its entire value chain. Obviously, a large amount of time and effort will be required by Amgen to reach this stage, and the work once that stage is reached is never-ending.

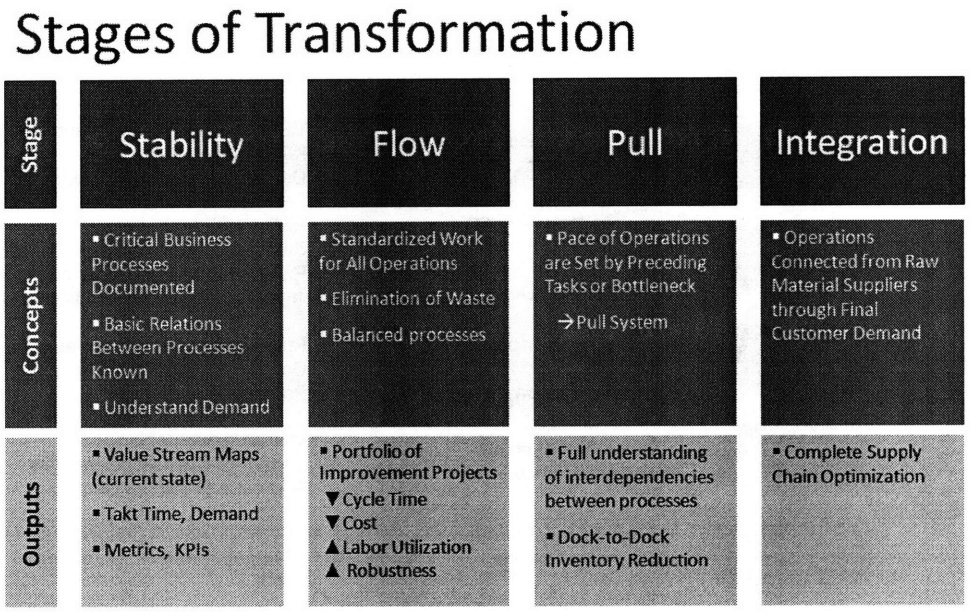


**Figure 4: APEX Stages of Transformation (Maturity Model)**

[29] These stages are based in part on those proposed by Womack and Jones – Value, the Value Stream, Flow, Pull, Perfection. (Womack & Jones, Lean Thinking, 2003)

The Operations Improvement team also provided a recommended deployment approach for the newly created APEX methodology – the Building Block approach. The building block approach to APEX deployment relies on a simple concept of dividing Amgen's operations into successively smaller groups until you arrive at a single existing operating team, referred to as a building block. Once that team is identified, they would then begin to apply the APEX methodology to issues in their areas, with the assistance of a process improvement coach if needed. As each building block uses the APEX approach, pockets of improvement can form which could in turn drive improvements between connected building blocks, throughout a production area, throughout a site and ultimately throughout the entire network. A pictorial representation of the initial stage of this approach is shown in Figure 5.

The utilization of the building block approach to APEX deployment has several key advantages. First and foremost, it allows for improvement efforts to occur at the shop floor level where the processes occur. This is critical for the success of any APEX effort, as the true expertise in operations lies with those who execute the tasks every day. Secondly, it helps to drive 'quick wins' which in turn drives momentum for the APEX efforts. Finally, it provides corporate management the ability to segment the operations network into observable functional units which helps with the overall program management and ability to drive efforts.

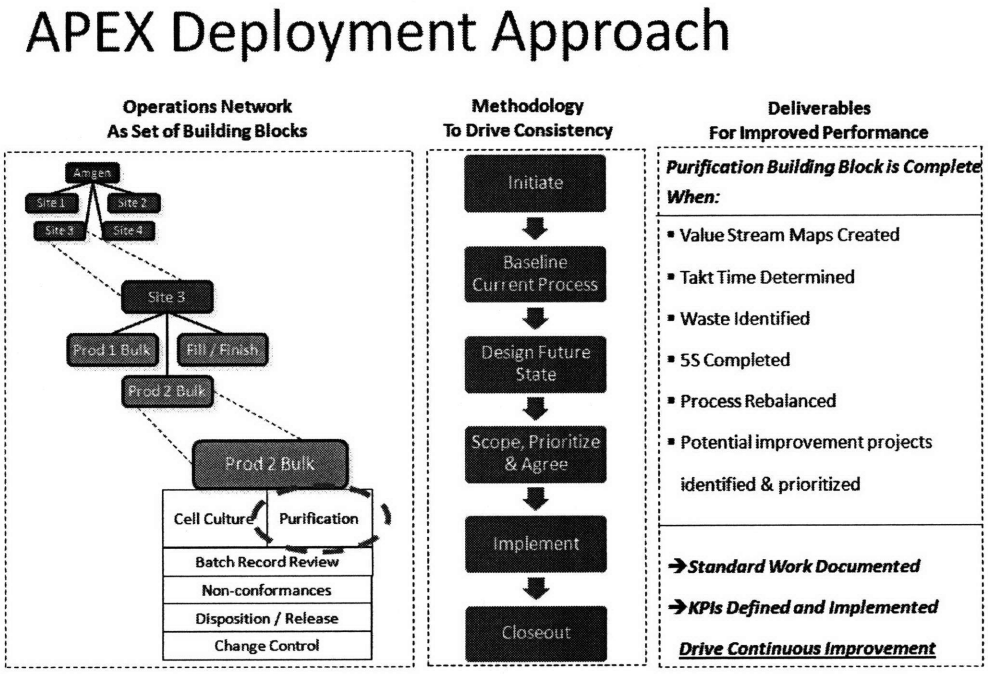


**Figure 5: Process Excellence Deployment Strategy**

## 4.3. Curriculum Development

In parallel with the development of the APEX methodology, the Operations Improvement team, including the author, began to create and assemble training modules to instruct leaders and operators throughout the Operations division on the core concepts of the methodology. The training modules, while often simple in content, needed to fulfill several key requirements and were vital to the success of APEX. First and foremost, they needed to effectively describe the tools and how they should be employed within Amgen. Secondly, examples within the modules had to reflect the operations environment within the biotech industry, as the use of 'assembly line' examples at any stage could be used by detractors of APEX as proof that the lean tools did not apply to Amgen's business. Finally, the modules had to be thorough yet brief, as the trainees had little time to spare away from their daily operations jobs. This restriction was taken very seriously by the APEX team, and was the driving force behind the structure of the training modules. As a result, the team sought to deliver the initial training on APEX in a week or less for the main implementers, and in one day or less for operators and management.

The training week was designed to have a flow to match that of a typical engagement with a new site or project team using the APEX methodology. The concepts would build throughout the week, starting with project kick-off tools and moving on to mapping activities and various other analyses. The week is comprised of different modules and exercises on several tools that are commonly used in process improvement activities (such as Waste Identification, 5S, Overall Equipment Effectiveness, etc.), with all content provided in binders for future reference.

### *Additions to the Training Week*

While these training modules were created using Amgen/biotech examples, they still in many ways represent the 'classic' way of looking at process improvement tools. To address this training issue, the APEX design team augmented the training week schedule to include two additional features.

First, the members of the team from Amgen's Rhode Island (ARI) facility offered the use of a process simulation that they had designed for training at the ARI site. This simulation was different from the standard Lego™ block assembly or paper airplane simulations often used in lean training, and instead mimicked a typical biopharmaceutical manufacturing process. The

simulation was the result of a large amount of effort from the ARI site, and contained all aspects of manufacturing in a regulated environment. These included, for both the 'current' and 'ideal' states, documents and visual resources on raw material procurement, manufacturing batch records, standard operating procedures (SOP's), quality testing and vessel cleaning among others. By incorporating sufficient detail and complexity into the simulation, ARI was able to circumvent the common pitfalls of unrelated process improvement simulators and instead focus on teaching the tools needed to address the issues. This biotech-based simulation was immensely effective in teaching the lean concepts to everyone from operators to management.[30] The APEX team was able to leverage this fantastic work performed at the ARI site and integrate it seamlessly into the training week schedule. The simulation now provided employees undertaking the training the opportunity to apply the modules just covered to a situation that resembled the processes at their home facilities. This helped to drive home the lessons learned in the training week and also served to motivate the trainees to apply those lessons when they returned to their sites.

Second, with help from the APEX team, the author designed a case study based upon a real-life issue faced at one of Amgen's sites (refer to Appendix A). The case study exercise was placed at the end of the training week to serve as a capstone to the course, and solidify the applicability of the APEX tools and methods. The case study presents a situation where a site needs to decide whether it will have enough capacity to meet demand for a product within the existing facility, or if an expansion is needed. Data that would normally need to be gathered at a typical APEX engagement are presented to the trainees, but the analysis of that data still needs to be performed. To simulate using APEX at their sites, the case exercise was performed in small break-out teams of 3 – 4 trainees. While the problem appears difficult at first, the use of the APEX approach simplifies the issue and allows the teams to identify potential solutions in a short amount of time. Following the case study, the facilitators lead discussions with the teams to discuss where they had difficulties, what tools were applicable and to reflect on the lessons learned from the case. Through the use of this case study along with the biotech-based process simulator, the APEX training week solidified the applicability of APEX to Amgen's manufacturing sites.

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[30] For more information on the development and execution of the ARI process simulation, refer to Shonna Coffey's LFM thesis "Achieving Business and Operational Excellence in the Pharmaceutical Industry" that details her experiences working at the ARI site on operational excellence.

## 4.4. *Analytical Tool Development*

As the APEX methodology was in development, it became clear that certain analyses were considered basic elements of any improvement efforts, specifically in assessing the current state of operations and identifying and prioritizing opportunities for improvement. To facilitate the repetitious nature that these analyses would come to represent and to provide a standard APEX format, some limited analytical tool development was added to the APEX development work stream.

### 4.4.1. Process Run-Rate Analysis Tool

During the initial roll-out of the APEX methodology at LakeCentre (discussed in section 5.1.1), a visual representation of the different operations involved, including their lengths and interdependence, proved to be a very useful tool for identifying process bottlenecks and opportunities for process improvement. The information contained in the chart is a basic starting point for any process analysis and is explicitly required in the early stages of the defined APEX methodology. Given that this display of information was proven to be useful and that it would be repeated multiple times throughout the network, it was proposed that the chart be automated into a tool that would minimize user effort while still providing the information in pictorial form. The Process Run-Rate Analysis tool provides simple, easy-to interpret charts that graphically demonstrate the interdependencies among operations during the production of an individual product at a particular site. The tool was created in Microsoft Excel using Visual Basic for Applications (VBA) to ensure ease of use and company-wide access to the program. While much of the information provided within the charts may be known within the site, the tool allows for the cohesive presentation of these data in a consistent manner across sites. In addition, the tool provides a graphical presentation of the data that is not currently found, which proves to be very useful in identifying potential process bottlenecks and potentials for nesting in between batches.

*Data Sources and Entry*

The charts in the Process Run-Rate tool are constructed based on user-entered data about the specific process being investigated. In constructing this tool, the Operations Improvement team decided to rely upon an existing source of information that was already present throughout the network known as the finite schedule. A few years prior to the present APEX effort, there was another initiative within Amgen that began to standardize certain processes and computer systems throughout the company. One of the key successes of that initiative was the use of *finite schedules* at each site for each of their products. These schedules included a detailed breakdown of all of the discrete production steps and the time and resources required at each step for the production of a single batch of a product, from the dispensing of raw materials to the transfer of the drug substance into storage. While the original intention of these schedules was to assist in planning of resources and material scheduling, the data provide a clear basis for manufacturing scheduling, plant capacity and overall flexibility. An additional benefit of using this established source of data, aside from its network-wide availability, is that the accuracy of the numbers provided was removed from any possible critiques of the tool. If a manager wished to criticize the results of the Process Run-Rate Analysis tool based on the data provided, they would have to then update and improve the time estimates provided in the finite schedule. This would result in more accurate data for everyone, and would still point the group towards areas for improvement within the process. These revised data would also allow managers to evaluate and address any variability in the times for the discrete production steps. Given that the Process Run-Rate tool allows for the rapid creation of charts depicting the process flow, managers could easily create charts using average, minimum and maximum times to target which variances have the largest impacts on overall processing time.

The User Input screen for the Process Run-Rate tool is shown below in Figure 6.[31] The user can input the process, existing run-rate (days between starts) and process steps. Within each process step, the user then enters the time associated with the steps sourced from the finite schedule. For this purpose, the tool specifies three time periods associated with each step to aggregate the time required. First is preparation time, meaning the time required to prepare the

[31] Data depicted in this section does not represent actual Amgen process steps, run-rates, production times or support system capacity and is for illustrative purposes only.

process equipment to receive the in-process product (cleaning, calibrating, etc.). Next is process time, which covers the time during which the protein product is present within the process step. This period was specified in this way to eliminate any ambiguity in the determination of where to allocate time in the tool. By specifying only that the protein product is present in the unit operation (process step), there are no debates over when the "value-added" operations start and stop, and the data are then more easily compared across products. Last, the post-run time period includes all activities that occur on a process step after the protein has moved in the process. Often when a process is running at capacity these post-run operations directly precede the preparation activities for a product. For each of these time periods, users take the data from the finite schedule and aggregate the times according to the definitions outlined above. For each unit operation, the user enters the total time per period (from the start of the first activity to the end of the last activity in clock time) and the "compressed" time per period (the sum of all activity lengths without regard to delays). The purpose of these two distinct entries will be discussed later.

| | A | B | C | D | O | P | Q | R |
|---|---|---|---|---|---|---|---|---|
| 1 | Product & Area | Wondergen Pur | | Create Run Rate Chart | Create Compressed RR Chart | | | |
| 2 | Run Rate (Days) | 4 | | | | | | |
| 3 | Max Effective Process Run Rate (days) | 1.7 | | Create Max Run Rate Chart (Support Constrained) | Experiment with Run Rates | | | |
| 4 | Float between Nests (hours) | 0 | | | | | | |
| 5 | | | | | | | | |
| 6 | Wondergen Pur 4 Day Run Rate | | | | Compressed Schedule | | | |
| 7 | | Prep | Process | Post-Run | Prep | Process | Post-Run | |
| 8 | Homogenization | 1 | 5 | 6 | 1 | 5 | 6 | |
| 9 | Centrifugation | 3 | 15 | 3 | 2 | 15 | 3 | |
| 10 | Oxidation | 1 | 20 | 4 | 1 | 19 | 4 | |
| 11 | Depth Filtration | 3 | 4 | 4 | 3 | 3 | 4 | |
| 12 | Chromatography 1 | 24 | 5 | 12 | 24 | 5 | 12 | |
| 13 | Chromatography 2 | 9 | 8 | 6 | 8 | 5 | 5 | |
| 14 | Chromatography 3 | 6 | 17 | 17 | 6 | 9 | 17 | |
| 15 | UF/DF | 11 | 6 | 6 | 11 | 3 | 6 | |
| 16 | Final Filtration | 2 | 3 | 4 | 2 | 3 | 4 | |
| 20 | Support System | Units | Usage per Batch | Availability per Day | | | | |
| 21 | WFI | gallons | 185000 | 71000 | | | | |
| 22 | PUR | gallons | 410000 | 205000 | | | | |
| 23 | Pur CIP | Cycles | 43 | 16 | | | | |
| 24 | Ferm/IB CIP | Cycles | 11 | 12 | | | | |
| 25 | Buffer Prep 1 | Batches | 6 | 3 | | | | |
| 26 | Buffer Prep 2 | Batches | 7 | 3 | | | | |
| 27 | Autoclave | Cycles | 13 | 12 | | | | |
| 28 | Labor | Hours | 1050 | 384 | | | | |
| 29 | | | | | | | | |
| 30 | Staff per Shift (average) | 16 | | | | | | |
| 31 | Shift Length (hours) | 8 | | | | | | |
| 32 | Shifts per Day | 3 | | | | | | |
| 33 | | | | | | | | |

Notes on Use

1. All values for Run Rate and Desired Run Rate must be entered in days. All data for the process steps or "float" must be entered in hours.

2. The Max Process Run Rate Chart (Process Constrained) does not account for overutilization of support systems. The Max Run Rate Chart (Support Constrained) accounts for both process and support.

3. Use a different version of this spreadsheet per product to avoid re-entry of data and confusion between chart outputs.

4. The maximum effective run rate is based on process length restrictions, not physical layout or process restrictions. This value can be adjusted using the float value directly beneath the max run rate.

**Figure 6: Process Run-Rate Analysis Tool – User Input Screen**

Below the entry area for the specific production process are several *Support System* processes that also provide valuable information on how the production process operates within the facility. The support systems listed in Figure 6 above represent typical systems that govern production rates at manufacturing facilities, but can easily be modified for specific systems known to be issues at a particular facility. To understand how this portion of the tool functions, refer to the "WFI" entry in the Support System section of the user input screen. WFI, an abbreviation of water for injection,[32] is generated at the manufacturing facility for use in the manufacturing process. The WFI generation capacity for the facility is limited by the size of the installed equipment, and is usually represented as the maximum total volume produced in a given day. The example shows a WFI generation capacity of 71,000 gallons per day.[33] This facility based information is then compared with the process based information concerning the total WFI demand to produce one batch of product. These volumes are known from the automation systems that clean equipment and from formulation records that dictate volumes for compounding, and are shown in the figure to total 185,000 gallons per batch of Wondergen. This information then provides the user with a rough estimate of the fastest potential run-rate for the product with respect to the WFI generation support system. Similar figures are collected for other systems (from documentation or automation) to provide a complete picture of capacity. Once the user has entered all of the process and support system related data into the Process Run-Rate tool, the tool is then able to generate charts for different run-rate scenarios.

***Current State Run-Rate Chart Output***

The first chart created by the Process Run-Rate Analysis Tool is the output that represents the Current State of production, shown in Figure 7. This chart offers the user an opportunity to quickly scan the results to ensure the accuracy of the entered data as it represents their current operating mode. To introduce the output from the tool, it may help to divide the chart into two zones, the Process Detail Zone and the Support System Detail Zone (highlighted in Figure 7).

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[32] Water for injection (WFI) is a highly pure grade of water produced by reverse osmosis or distillation with the standards for production (chemical and microbial quality) governed by the United States Pharmacopeia (USP). (Edstrom Industries, 2008)

[33] For multi-product facilities, the generation capacity is sometimes provided as gallons per day per product.

The Process Detail Zone is based upon the data provided from the finite schedule and consists of a graphical representation of the production process. All of the bars in the chart output are scaled according to their associated time requirements, to provide an easy visual check on the most time-intensive process steps. The blue Run Rate Length bar shows the total time required to produce one batch, while the green Critical Path Length bar dictates the total time required for processing the protein product and excludes preparation and post-run activities. The orange Float bar demonstrates the flexibility built into the process to allow for any delays in production that would still allow the run-rate to be met. Within each process step, there are three bars representing the different activities for that step along with the time required per the finite schedule. The numbers shown in parentheses are the compressed time requirements for that step. To show the dependencies between process steps, arrows are displayed to demonstrate the flow of the intermediate protein product throughout the process. The tool relies on these dependencies to display the timing of each step for an individual batch.

The Support System Detail Zone is a simple bar chart that provides the utilization rates for each support system based on the provided data. The bars are color-coded to draw the user's attention to systems that are being heavily utilized. Green bars represent systems that are below 70% utilized, yellow signifies 70 – 85% utilization and systems greater than 85% utilized are displayed in red. The systems displayed in Figure 7 are all green, showing that the existing run-rate for Wondergen does not overly tax the support systems during a typical production run. This fact, along with the 13 hour float in production, demonstrates that the facility is very comfortable running at the existing run-rate for Wondergen. This is to be expected, as the data used to generate this output comes from the finite schedule which was designed with this specific run-rate in mind. While this output is valuable in representing the existing processes in a simple one-page format, the true value of the Process Run-Rate Analysis tool comes when attempting to modify the run-rate and identifying potential bottlenecks that may arise.

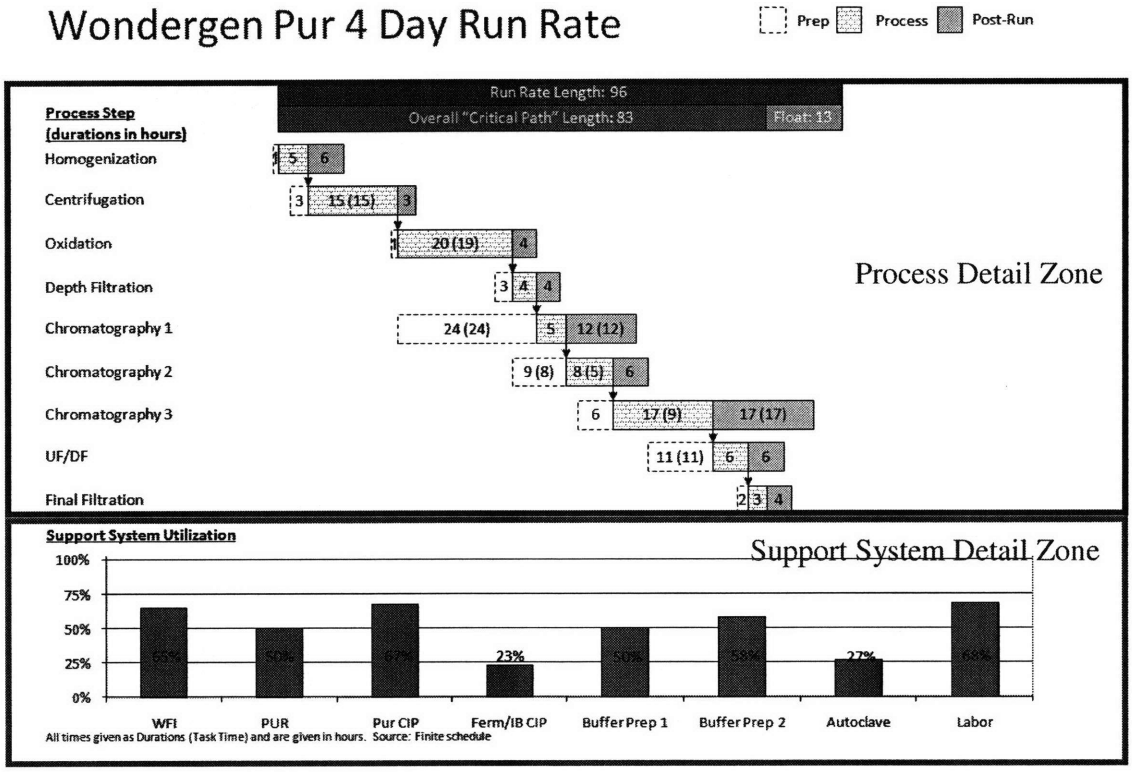


**Figure 7: Process Bottleneck Analysis Tool – Current State Run Rate Output**

### *Alternate State Run-Rate Chart Outputs*

The tool has three alternate chart outputs to help the user explore potential run-rate scenarios: Compressed, System Constrained and Desired run-rates. In these scenarios, the process steps and their associated time bars are color coded in a similar manner to the support systems, with the only difference being that below 70% utilization they appear in the standard format of the Current State chart.

The Compressed Run-Rate chart, shown in Figure 8, demonstrates the effects of running the process using only the compressed time values from the finite schedule. In the example shown, none of the process steps become rate limiting at that run-rate, but the WFI, CIP and Labor utilization rates are shown increase to almost 100% capacity. This provides the user or manager a clear picture of which systems (in this case) or process steps must be addressed and optimized to run at this compressed run-rate.

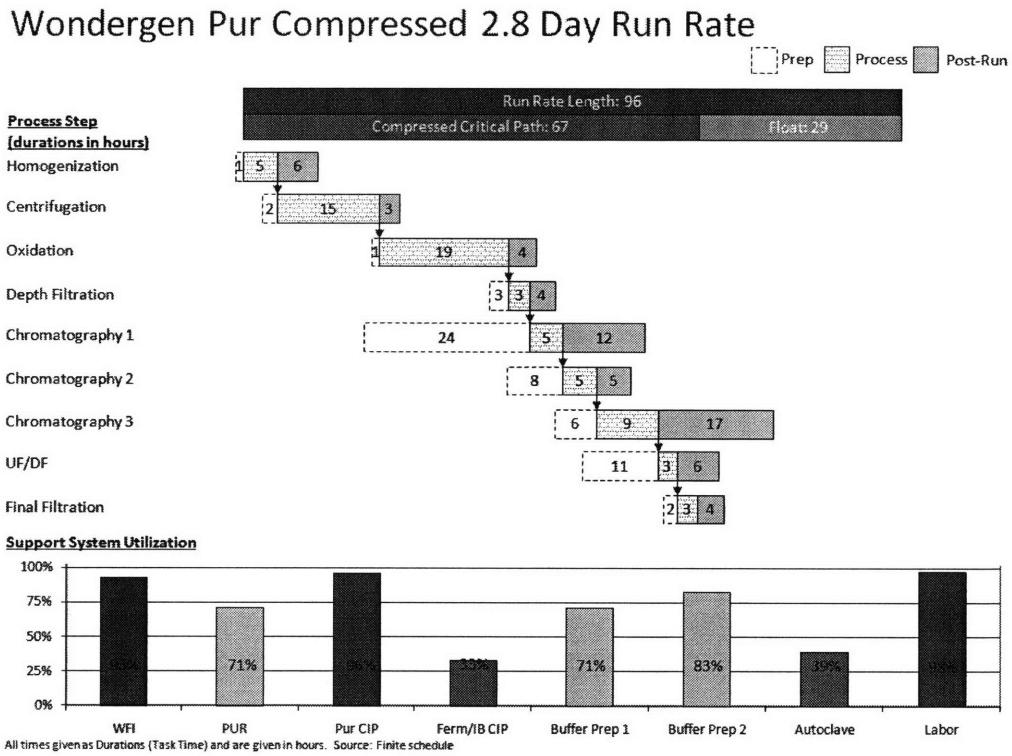


**Figure 8: Process Bottleneck Analysis Tool – Compressed Run Rate Output**

The System Constrained Run-Rate chart, shown in Figure 9, uses the data provided for both process and support systems to determine the fastest possible run-rate. The tool identifies these limits as either the rate at which the end of post-run activities equals the start of preparation activities for an individual process step or when any single support system reaches 100% utilization. In the example shown, Labor utilization reaches 100% and proves to be the bottleneck for increasing the run-rate for the process further. Again, the output proves to be a valuable tool for the manager in that it is seen that once the Labor utilization is addressed, other systems, and therefore other bottlenecks, will quickly become the rate limiting steps.

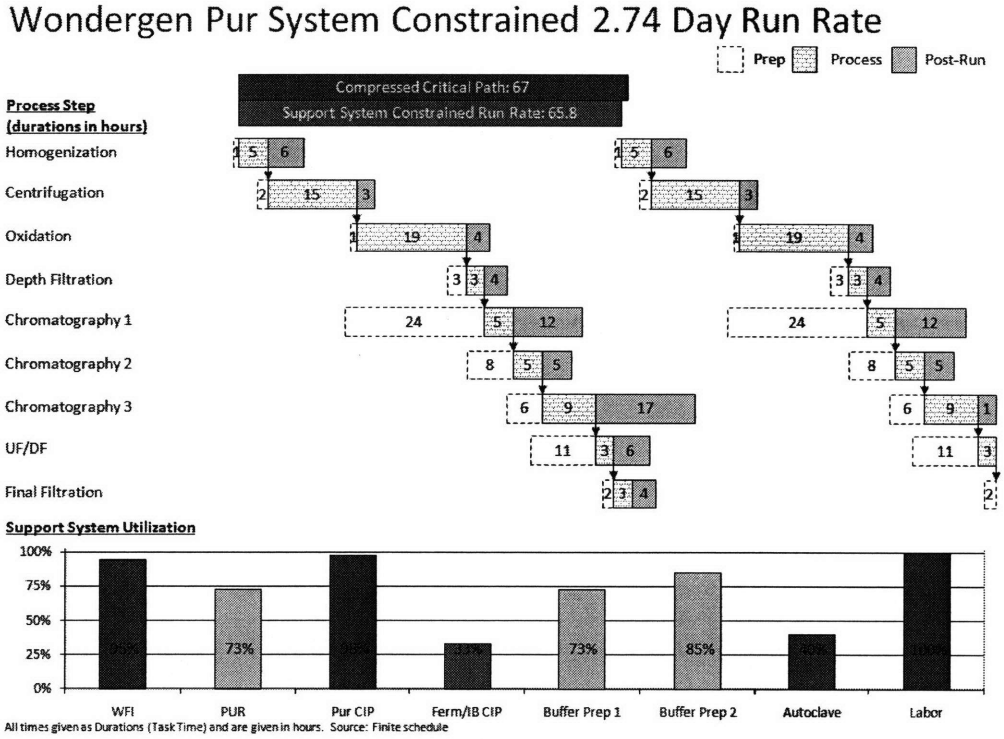


**Figure 9: Process Bottleneck Analysis Tool – System Constrained Run Rate Output**

The final, and perhaps most valuable, output from the tool is the Desired Run-Rate chart. This chart, shown in Figure 10, allows the user to enter any desired run-rate for the process and to then observe which process steps or support systems must be modified or addressed to achieve them. The only restriction on the user-input for this chart is that it must be greater than or equal to the minimum effective time required to process one batch. This restriction was included because a change in the manufacturing process is both difficult and costly, and may in fact not even be a possibility. The real value for this output is its flexibility, as users can enter run-rates that are *shorter* than the current process or *longer*, depending on the needs of the facility and demand for the product. A user can experiment, at low granularity, with the impact on labor of different run-rates and can contemplate a change in staffing levels or shift structure to balance product demand and production requirements. This can help to determine how to allocate production staff among different products within a facility and properly utilize plant capacity. As with all of the tool's outputs, these charts are only a first step in the investigatory process that help to direct management to the areas that need further investigation and refinement.

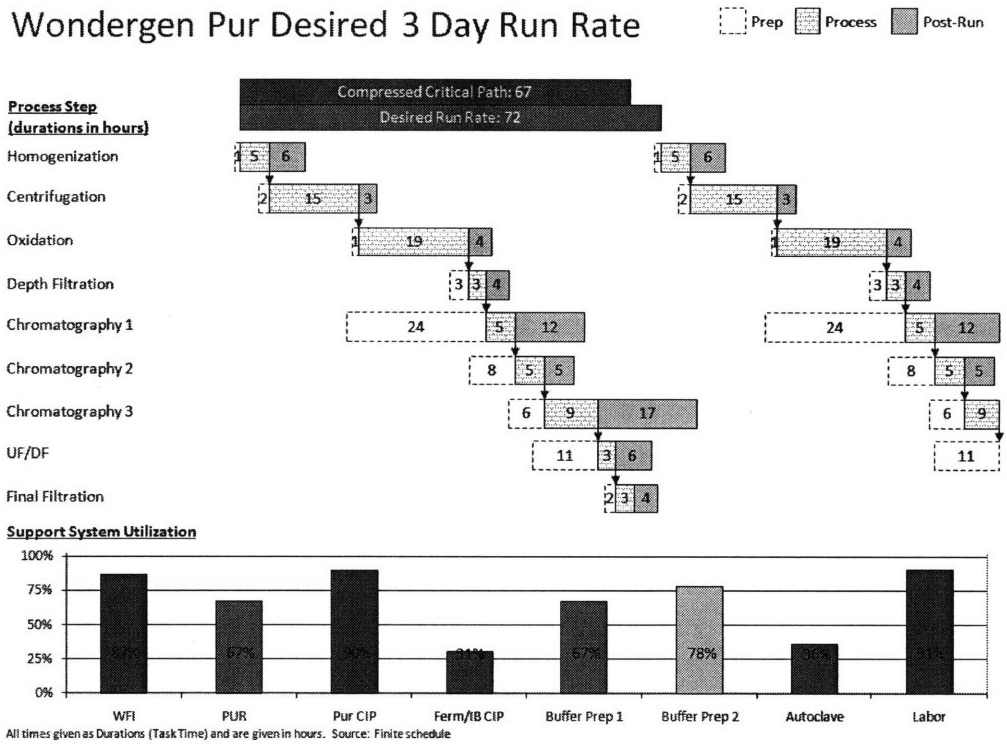


**Figure 10: Process Bottleneck Analysis Tool – Desired Run Rate Output**

### 4.4.2. Process Lead Time and Inventory Allocation Framework

The Process Run-Rate Analysis tool was developed to help target improvement areas within a specific segment of the production process for a product, such as fermentation, cell culture or purification. While improvement efforts can increase the efficiency of these specific areas, these improvements may not necessarily improve the efficiency of the entire production process if they are not, at an area level, rate-limiting. In order to address the selection of the correct areas to target with improvement efforts, an additional analytical tool was initiated to assess process lead times and inventory allocation. This tool was added to the APEX development work stream very late during the project, and as a result is at a very early stage of development in comparison with the Process Run-Rate Analysis tool.

The Process Lead Time and Inventory Allocation framework was designed to capture high-level information about the entire production process that should be visible and known throughout the production supply chain. The main thought behind this framework was to increase awareness about the impact of individual area lead times and variability on the overall process lead time. As this awareness was increased, managers would be able to direct efforts to improve overall performance of the production process and set work-in-process inventory levels that accurately reflect the process limitations and needs.

Figure 11 is an early proposed version of the framework template for use as part of the APEX process applied to the fictional Wondergen product. For an individual product, the owner of the overall improvement process would contact individual process owners for information regarding cycle times, inventory targets and required service levels (if known). The cycle time data are equivalent to the current run-rate discussed previously in section 4.4.1, only in this instance the framework is asking for actual achieved cycle times (both average and standard deviation) rather than the target. The user of the framework will likely need to contact representatives in the finance and supply chain groups to obtain information regarding inventory costs and targets to complete the required information. Qualitatively, the collection of the information for the framework on its own will help to direct efforts of the improvement team based on the magnitude of the associated costs or impact of individual cycle times on the overall lead time for the product. Quantitatively, the data collected can be fed into a software application to help determine appropriate inventory levels for work-in-process inventory based

upon process performance and service levels. The framework itself is based upon the data requirements for Optiant's PowerChain™ Inventory software which the author used during his coursework on supply chain planning. An example of how the framework would translate to the software application is shown in Figure 12 and demonstrates the consistency of icons and required data.


| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Average Cycle Time (days)[1] | 30 | 10 | 30 | 4 | 30 | 4 | 30 |
| Std Dev Cycle Time (days)[1] | 15 | 1 | 15 | 1 | 15 | 1 | 15 |
| Cost of Inventory ($/g) | 200 | | 4000 | | 8000 | | 12000 |
| Current Inventory Target (days) | 60 | | 45 | | 45 | | 180 |
| Current Service Level (%) | 100 | | 100 | | 100 | | 100 |
| Required Service Level (%) | 95 | | 95 | | 99 | | 100 |
| Proposed Inventory Target (days) | 45 | | 30 | | 30 | | 120 |

[1]Cycle Times for Inventory Stages include Disposition Activities

**Figure 11: Process Lead Time Framework**

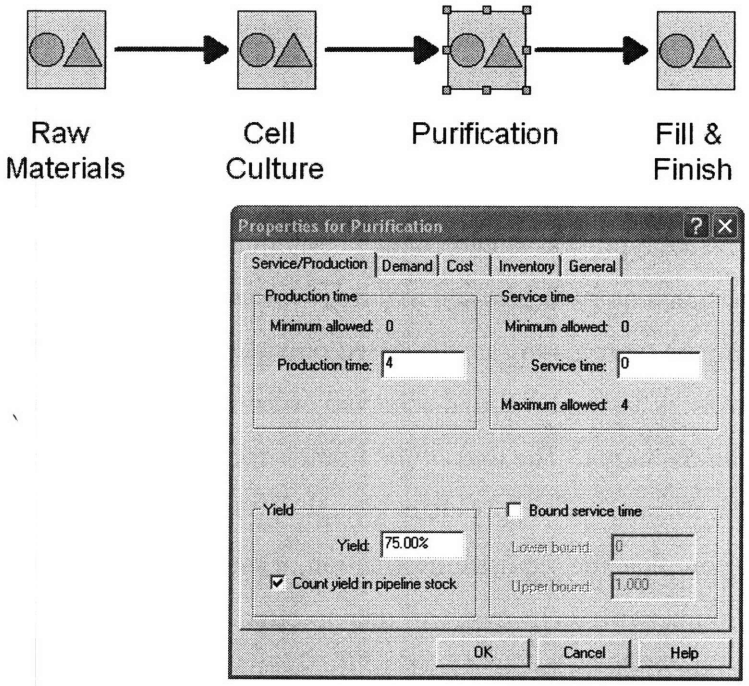


**Figure 12: PowerChain™ Inventory Model of Wondergen Manufacturing Process**

# 5. Initial Implementation Activities at Manufacturing Sites

In parallel with the development of the APEX methodology, the Operations Improvement group sought to validate the approach by exercising the main concepts and tools at Amgen manufacturing sites. In essence, the team sought to walk the walk of continuous improvement and to ensure that what was being proposed would be effective within Amgen's plants and culture. During and following each of these initial implementation activities, the Operations Improvement team updated and improved the APEX system to reflect the lessons learned while at the sites. All of this was done in the spirit of having a continually improving continuous improvement methodology. As with other examples in this thesis, the data and findings in the following case studies have been disguised to protect confidential Amgen information.

## *5.1. Amgen Colorado, LakeCentre Site Activities*

Amgen Colorado is comprised of two manufacturing facilities, Longmont and LakeCentre, which manufacture several commercial products as well as late-stage pipeline candidates. The LakeCentre facility produces Kineret® (anakinra), Kepivance® (palifermin) and other pipeline product candidates utilizing its large scale, multi-product and multi-host facility.[34] The designation of multi-host is significant, in that it denotes a facility with robust validation and cleaning procedures that allow it to manufacture both microbial and mammalian based products using common equipment. This designation is not without its challenges, as will be discussed, but does place the LakeCentre facility as a key center in the future of Amgen's Operations.

The opportunity to participate in site-improvement activities at LakeCentre arose in the preliminary stages of the development of APEX. Site leadership had already undertaken an effort to examine their internal processes and identify potential opportunities for improvement and savings. Members of the Operations Improvement team were already in contact with LakeCentre leadership about the APEX effort, and when this opportunity arose it was proposed that this effort be used to test some of the tools and methodologies under development.

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[34] (Amgen - Careers - Campuses, 2008)

It is important to distinguish that the site efforts at LakeCentre were tasked with *identifying* potential opportunities, not implementing improvements at that time. The site had existing mechanisms for implementation, and wished to rely on those systems for implementation following the identification process. The Operations Improvement sub-team was invited to the site to participate in deeper analysis of two identified issues: Clean-in-Place (CIP) utilization and Changeover (switching between products) activities. Again, any recommended projects would then proceed through normal site governance if chosen for implementation.

### 5.1.1. Process Bottleneck Analysis and Overall Equipment Effectiveness

The first focus area for the Operations Improvement sub-team involved a thorough analysis of the Clean-in-Place (CIP) system in the Purification suite. The CIP system is a primary support system in the manufacturing of protein therapeutics with a primary function of cleaning large scale equipment that cannot be moved for cleaning. Examples of the types of equipment requiring CIP are product vessels, buffer (solutions) vessels, filtration or chromatography skids and transfer lines between vessels. In the case of the LakeCentre facility, the CIP system also provided the controls and pumps for the Clean-out-of-Place (COP) baths, the system used to clean all parts that can be moved for cleaning. As a result, the CIP system in the Purification suite was the support system for nearly all cleaning activities and was generally accepted throughout the site to be the main bottleneck and run-rate-limiting step for all purification products. Several improvement initiatives were already underway to address this issue, however the Operations Improvement team was tasked with identifying alternative approaches and evaluating current efforts.

Although the team could observe that the CIP system utilization was an issue to be addressed, a cycle time analysis was performed first to confirm that it was the true process bottleneck. In addition, the cycle time analysis would simplify the presentation of different production scenarios that could be possible with different process improvements. To perform the cycle time analysis, interviews were conducted with different process experts as well as the site planners who owned the finite schedule. The end result of these interviews and available schedule information was a clear breakdown of the time required by each unit operation into preparation, process and post-process segments for a single run. The team also collected information about the primary support systems to understand their demand per production run.

The information was then presented in a graphical format that would depict the order of steps, the flow of protein intermediates and support system usage. During this engagement, the graphical representation was created in Microsoft PowerPoint and involved manually positioning and sizing the different bars to reflect a consistent scale, taking several hours to complete once the data were collected.[35] The final output from this analysis is shown below in Figure 13 (process steps disguised and data omitted to protect confidentiality).

Several key learnings were obtained from the initial cycle time analysis. First, it reaffirmed the site's perception of the CIP system being a process bottleneck, with a scheduled utilization of 85%, and showed the potential impact of specific improvement efforts currently underway. Second, it showed that the buffer preparation time for the process was likely to become the new process bottleneck as process improvement activities occurred on the CIP system.

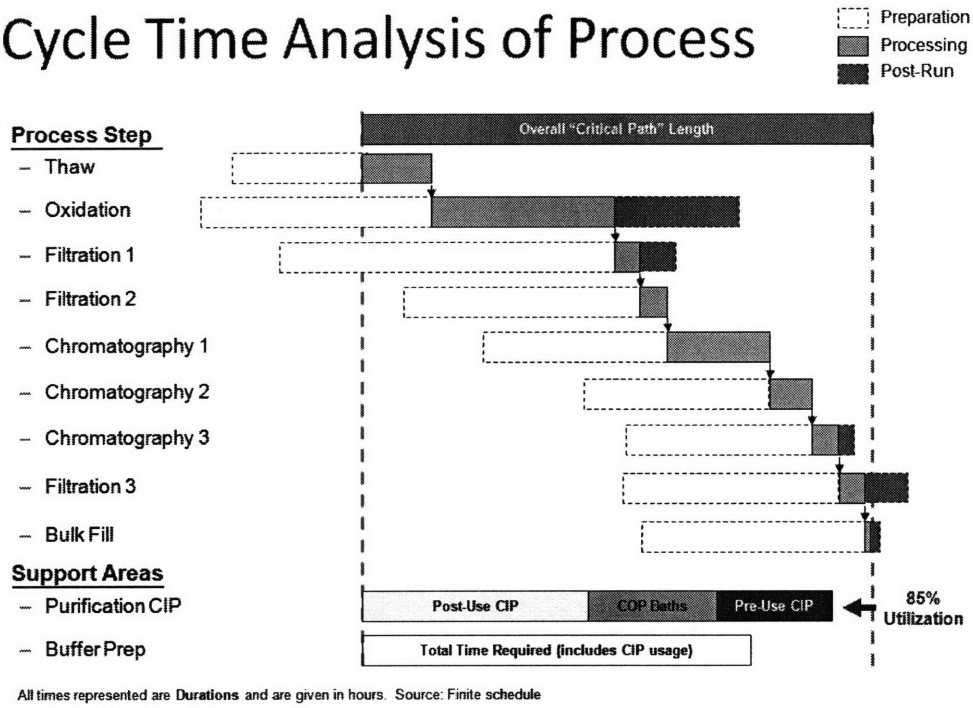


**Figure 13: Amgen Colorado Process Cycle Time Analysis**

[35] The end value of this graphical output, and the amount of labor it required for construction, was the motivation for the automated Process Run-Rate Analysis tool discussed in Section 4.4.1.

Following the creation and review of the cycle time analysis performed, the next task was to dive into the day to day operations of the CIP skid to verify the predicted utilization numbers from the cycle time analysis and identify potential areas for improvement. The verification step was critical as all of the initial analysis was done using time estimates, mainly from the finite schedule and process owners. By investigating the actual usage data, the team will be able to determine how accurate the schedule is for the process bottleneck and find the magnitude of the problem being addressed. The optimal approach for obtaining actual usage data would be the direct observation of the process. Unfortunately, the manufacturing facility was in shutdown during the group's time on site. This led the team to use the next best thing to direct observation, the usage of available historical continuous data.

As with most modern biopharmaceutical manufacturing facilities, LakeCentre utilized a Supervisory Control and Data Acquisition (SCADA) system for both process control and monitoring. SCADA systems electronically capture large volumes of data (flow rates, valve positions, pH, conductivity, etc.) at frequent time points from sensors installed throughout the facility's equipment. While SCADA systems are a fantastic repository of data, the sheer volume of measurements and sensors contained in the system can be overwhelming when trying to gather the specific data needed for targeted analyses. To circumvent this issue of too much data, most SCADA software packages also include additional software that samples and aggregates the raw data to produce workable datasets for analysis. Even with these reduced datasets, the sheer volume of sensors within each process step still proves daunting when attempting an analysis.

For the LakeCentre CIP analysis, the first step in the analysis (after obtaining access to the data) was to identify the available sensors on the CIP system. To perform this, the piping and instrumentation diagram (P&ID) for the system was reviewed. There was no single source of datum shown on the P&ID that showed whether the system was in use, so a combination of valves, flow meters and pump indicators was identified that would signify the start and stop of CIP cycles. Unfortunately, this would only indicate the processing portion of the CIP usage, not the set-up or break-down activities, but would serve as an adequate indicator of the process cycle time. The site had previously constructed a very useful data retrieval tool that accessed the aggregated data, and with the addition of the specified tags the analysis could begin.

The next step was to extract data for a known specified period of routine production to evaluate the performance of the CIP skid versus its scheduled operating time in the finite schedule. In addition, several other performance indicators were reviewed, including the effectiveness of chemical dosing pumps and the number of equipment initiated and operator initiated aborts during cycles. This data collection and analysis took approximately two days to collect and analyze, with the end product a representation of the CIP system performance using an Overall Equipment Effectiveness (OEE) metric.

Overall Equipment Effectiveness is a common metric applied in lean manufacturing and other continuous improvement programs. OEE provides a simple set of equations and graphical output that quickly informs managers and operators about the sources of downtime on a particular piece of equipment and the areas that need the most attention for improvement. The calculation of OEE that was used at LakeCentre is shown below in Equation 1 and is the product of utilization, availability, performance and quality percentages. Utilization, sometimes not included in OEE calculations, is a measure of the total planned production time for the plant itself. This is calculated at total available time (e.g. one year) minus the known losses due to holidays and shutdowns. The losses measured by this portion are termed *planning losses*. Next is availability, which measures the difference between the planned utilization and the amount of time the equipment is down for unplanned maintenance, referred to as *downtime losses*. Following availability is performance which represents the actual time the equipment is running in the time available. Losses for this measure are due to set-up and break-down activities as well as any loss due to running the machine at slower speeds than are possible, and as a result are referred to as *speed losses*. Finally is the measure of quality, which measures the ratio of time spent on successful runs to the total time spent running. The losses associated with this measure are called *quality losses* and represent aborted runs as well as runs that do not satisfy specifications.[36]

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

$$OEE\% = \frac{Planned\ Utlization\ Time}{Total\ Time\ in\ Period} \times \frac{Available\ Time}{Planned\ Utlization\ Time} \times \frac{Performance\ Time}{Available\ Time} \times \frac{Quality\ Time}{Available\ Time}$$

**Equation 1: Overall Equipment Effectiveness (OEE) Equations**

[36] (Vorne Industries Inc., 2008)

The data from the CIP system were analyzed and the losses were identified and grouped using the definitions outlined above. The resulting OEE visualization for the data is shown in Figure 14.[37] What was most surprising from the OEE analysis was how effective the site was at avoiding unplanned maintenance and, to a lesser extent, how minor the quality losses were. This contradicted some anecdotal evidence obtained from process experts who complained of frequent aborts on the CIP system. Indeed, the OEE values showed that the large majority of losses on the equipment fell into the unknown losses category, which reflected those losses that could not be accounted for using the available data. Within these unknown losses it is known, however, that the set-up and breakdown activities occur. Additionally, it is widely thought that inefficient scheduling of the CIP system could have contributed to some waiting time for the system, another example of a speed loss. These results showed a high potential for the site for debottlenecking the CIP skid through a focus on changeovers between cycles and improved scheduling. The clear messages provided by the metric led to its adoption by the site to help manage and optimize the CIP skid, with future efforts planned to observe the process while running to gain estimates around true set-up and break-down activities and plan specific improvement projects.

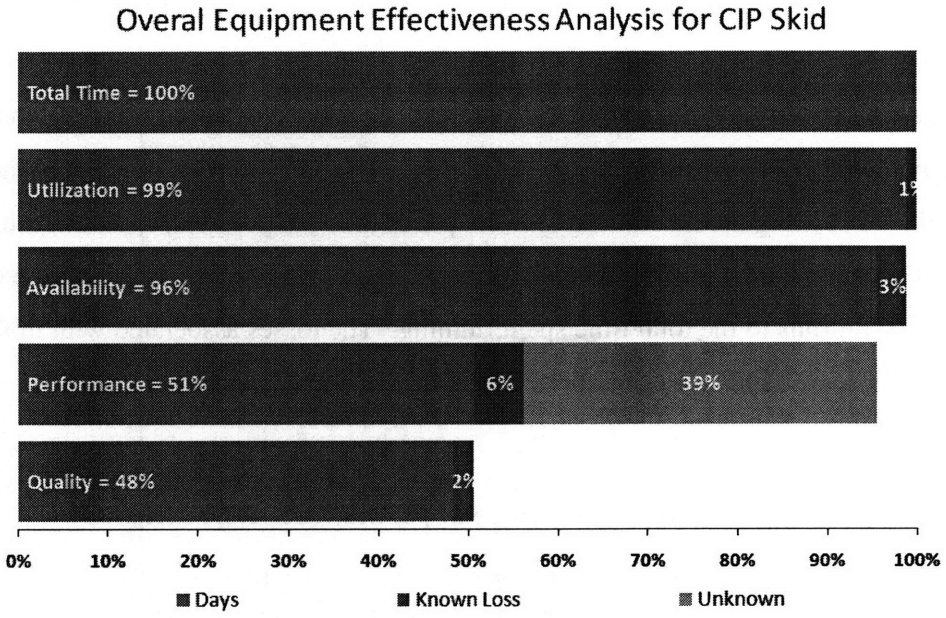


**Figure 14: Amgen Colorado Example of Overall Equipment Effectiveness Analysis**

[37] Data is disguised, but the general results of the analysis were preserved.

### 5.1.2. Acceleration of Changeover Activities

In addition to processing steps restricting the overall throughput of the facility, the changeover activities between products or hosts also caused significant delays. This was especially true when the facility was asked to produce multiple lots of different products in a year, and even more so when those different products were produced using different hosts. To address this issue, the team met with the key stakeholders throughout the facility that had a direct impact on the time requirements for changeover activities. The goals of the team were to provide a fresh perspective on the changeover process and to identify simple ways to improve the turnaround time.

The first meeting occurred with the facility's maintenance team to discuss the activities and staffing levels during the changeover period. The maintenance group was responsible for the equipment and parts change portion of the current multi-host changeover process detailed in Figure 15. These activities included movement of vessels, preventative maintenance and in some cases the change out of "soft" parts such as gaskets and plastic tubing. Currently these activities are performed by the maintenance team working 12-hour days. This led to the team's first recommendation of employing contractors to increase staffing and allow 24-hour coverage to vastly reduce the required calendar time for the activities. This change was evaluated using the existing finite schedule and showed a potential 17% improvement in total time.

Next, and in parallel with the first meeting, the team met with the planning personnel to review the finite schedule of activities. The combined group began to discuss the linear fashion with which tasks were conducted, and challenged some of the perceived limitations on parallel processing. Following discussion with some other minor stakeholders and quality personnel, it was proposed that the last two steps in the process, the Equipment/Parts Change and the Final Cleanings could be performed in parallel with minimal changes to documentation. This change, combined with the transition to 24/7 maintenance activities, could result in a 27% improvement in the required changeover time according to the finite schedule (see Figure 15). This translates directly to the overall availability and capacity of the LakeCentre facility, especially in years when multiple changeovers are required. These solutions were very cost-effective and did not substantially alter current operations, but led to real reductions in downtime at the facility. The group also proposed more work and capital intensive options, but these were tabled until the existing processes were optimized and evaluated further.

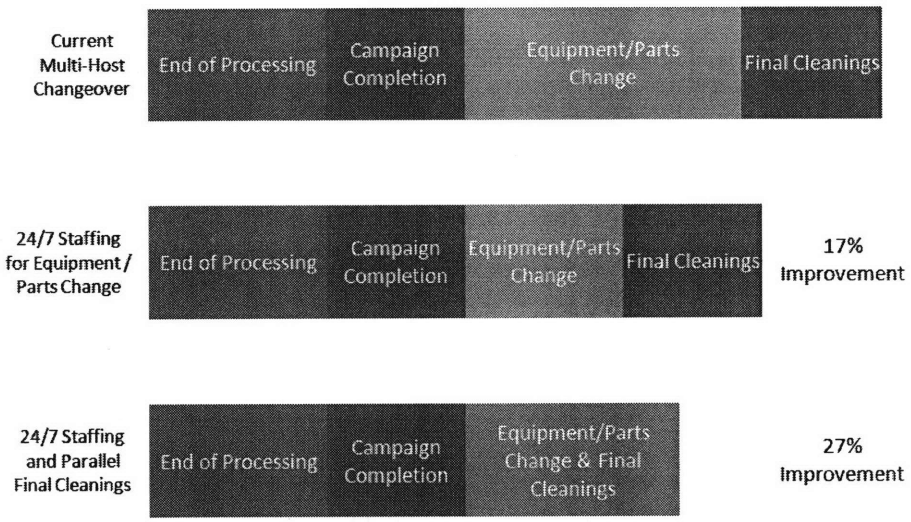


**Figure 15: Amgen Colorado Proposed Changes to Changeover Activities**

## 5.2. Amgen Fremont Site Activities

The Amgen Fremont manufacturing facility is a large scale, multi-product and multi-host facility that became part of Amgen Operations following the 2006 acquisition of Abgenix Corporation.[38] The facility was constructed by Abgenix for the production of Vectibix, now an Amgen product, but was built with flexibility in mind and is capable of making a wide variety of biological products at various scales.

A large driver of the Amgen acquisition of Abgenix was their partnership around Vectibix (panitumumab), which was thought by many to be a potential blockbuster drug in the oncology sector.[39] Although the drug is still gaining market share and helping more patients, it as yet has not achieved the sales projections that it initially held. Recent approvals in Europe for Vectibix may increase demand, however in the short term the management team at Fremont decided to assess the feasibility of manufacturing additional clinical or commercial products in their facility to increase resource utilization and to optimize their existing processes.

The APEX team, composed of members of the Operations Improvement group and other Amgen process improvement experts, was brought into the Fremont facility to help with these assessment efforts, and to participate in the initial improvement activities. Through these analyses and actions, the group hoped to validate the APEX tools and methodology as well as to help position the Fremont facility for future production of Amgen products. The first visit to the site was focused on the two initial steps outlined in the APEX methodology (see 4.2.2), specifically performing an initial assessment of the current state production using value stream maps and developing a potential list of improvement projects. Throughout the week, the group checked in with site management to ensure that the direction and focus of the team matched with the strategic goals of the site.

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[38] (About Amgen - Company History - Acquisitions, 2008)

[39] (Mitchell, 2006)

### 5.2.1. Lean Assessment of Site Processes

The team began its week long engagement at the site with a kick-off meeting involving all of the key stakeholders at the site, from plant management to subject matter experts (SME's) to production supervisors, to inform them of the purpose of the meetings throughout the week and to formalize the group's request for time from the manufacturing floor personnel. Following a brief window tour of the manufacturing facility, the group was ready to begin meeting with the site teams.

*Cell Culture Activities*

Given that the first task at hand for the team was to create value stream maps (VSM) for the production process, the first meetings were held with operators and managers from the Cell Culture suite. These employees are tasked with all aspects of the cell culture process for the product, from the initial thaw of cells through the different bioreactors and onto the purification process. Representatives from each stage throughout the cell culture process steps were gathered in a conference room with the APEX team to map the process. The team's initial goal was to have the group help to the team understand the set-up time, cycle time and labor content of step along with the interconnections between the steps and the flow of information. The team hoped to achieve this by having a discussion with the whole group over the course of 1 – 2 hours, asking them to rely only on their memory and the ideas of everyone within the group. This approach was wildly successful and resulted in a detailed VSM of the cell culture process within ninety minutes. A large part of the success in this session was the involvement of a senior Amgen manager with a strong background in lean manufacturing who led the event. In addition, several members of the APEX team, including the author, had relevant experience with manufacturing practices and known issues within both Amgen and the biopharmaceutical industry at large. This ability to rely on expertise in both lean methods and biotech manufacturing proved to be a critical factor in the success of this VSM effort.

The Cell Culture Value Stream Map is shown below in Figure 16. The data collected from interviews, the finite schedule and the site labor model helped to provide and corroborate the data presented in the VSM (process steps and times obscured to protect confidential information). Based on the mapping process, the combined APEX/Site team identified the Production Bioreactor and Harvest Operations as the key processes within the cell culture

process that should be the focus of the initial process improvement projects at the site. These process steps, when compared to the other Cell Culture processes, were selected due to the labor content required (resource constrained), overall cycle time impact (process/equipment constrained) and/or safety factors for the operators performing the tasks. The specific information behind these choices has been omitted for confidentiality reasons.

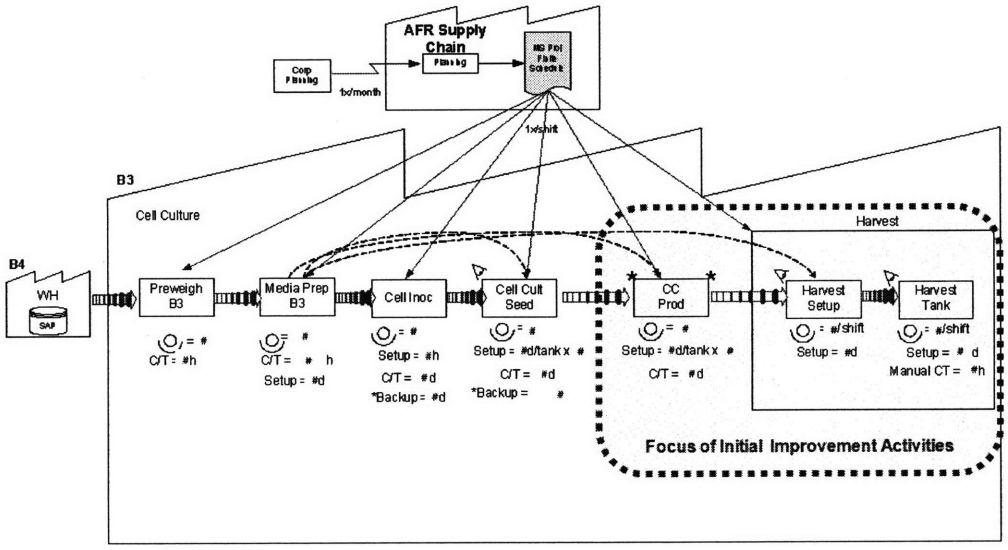


**Figure 16: Amgen Fremont Cell Culture Process Value Stream Map**

Following the creation of the VSM, the team led two discussion groups to create more detailed process flows and conduct brainstorming sessions for the Production Bioreactor and Harvest Operations process steps. The purpose of these activities was to gain better understanding of the specific issues faced by the operators, to generate lists of improvement ideas and identify pain points (labor difficulty, safety issues, etc.). This additional information, along with the original results from the VSM, proved to be quite valuable when the maps and proposed projects were later proposed to management. An example of the detailed process flow and focus areas for the Harvest Operations step is shown below in Figure 17.

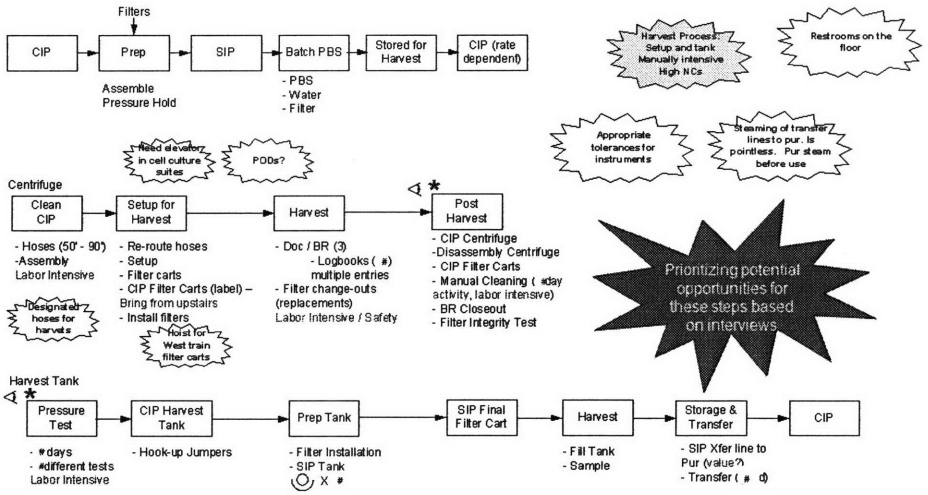


**Figure 17: Amgen Fremont Harvest Operations Process Flow and Brainstorm List**

*Purification Activities*

Following the group's first day capturing and describing cell culture activities, the next day was then devoted to the Purification suites. The same approach used for Cell Culture was employed with the operators, SME's and managers of the Purification areas. Following the initial meetings, the group was able to construct the VSM for the purification process, which had many more process steps and interdependencies than observed in the upstream process (see Figure 18 below).

The mapping activities and interviews revealed that no single unit operation required considerably more labor effort or time than the others, but that the support function of buffer preparation was the current bottleneck in the process. Through additional discussions with process experts, the buffer preparation process was shown to be the key enabler to increase flexibility and throughput for the suite, and therefore for the facility as a whole. These findings drove the proposed projects to be focused on increasing the utilization and performance in buffer preparation. The purification personnel helped to brainstorm lists of potential improvements ranging from simple improvements in process execution (defining and improving standard work) to small capital improvements that would alleviate bottlenecks on certain support vessels.

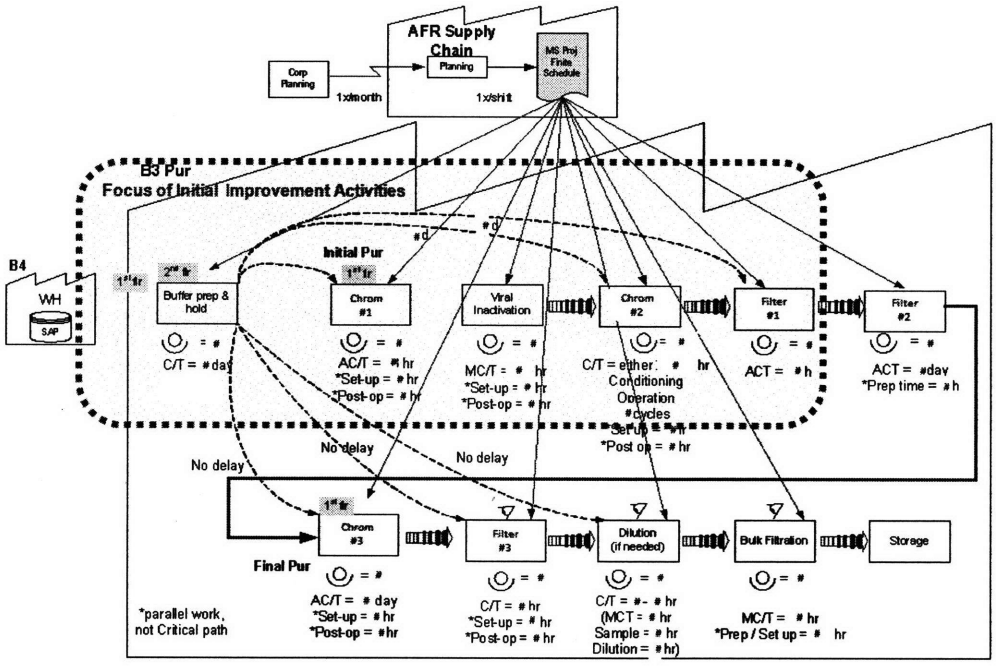


**Figure 18: Amgen Fremont Purification Process Value Stream Map**

### 5.2.2. Development of Potential Process Improvement Projects

The efforts of the combined APEX team and the site-based process experts were highly successful in kicking off the process improvements at the Fremont facility. Through the initial scoping meetings and value stream mapping sessions, the operators and managers became very motivated to begin improving their processes. This became even more apparent as the APEX team continued to focus on and lobby for the prioritization of improvements to those process steps and activities that were of most importance to them. In addition, the daily meetings with the site management team ensured that the goals of the APEX team were aligned with the long-term strategic goals of the site. With these initial steps completed and a base of support established, the team was now prepared to discuss the path forward at Fremont with the management team. These next steps were formulated based upon the next steps in the APEX methodology and were focused on the key areas identified during the week.

The team first proposed that another visit from a subset of the APEX team would be beneficial to both the team and the site. During this week-long visit, the team would refine the value stream and process maps for the targeted areas, adding more detail as needed. In addition, they would help with the prioritization of the brainstormed improvement projects from the previous visit, hopefully leading to the start of execution by the close of the week. Finally, specific APEX team members would begin providing training on the APEX tools and methodology to the staff in the targeted areas as well as the area management.

Subsequent to this follow-up visit, the APEX team would return again to finalize their assessment of the current state and to facilitate the implementation of the initial improvement projects. As was the case previously at LakeCentre, the Fremont facility was in shutdown during the initial visit of the APEX team. This prevented the team from having direct observation of the process, and it was vital that this be completed prior to any improvement projects to avoid extraneous work. In parallel with these observation activities, training on APEX would be made available to additional personnel at the facility to help encourage small-scale improvements in all areas of the site. The Fremont site management team was very eager to have their staff trained on APEX, as their goal was to initiate and foster a culture of continuous improvement at the site. Following these execution activities, another meeting between the APEX team and site management was proposed to determine the appropriate next steps for the facility.

## 5.3. Lessons Learned Through Initial Implementation Activities

The implementation activities at the LakeCentre and Fremont sites provided the Operations Improvement team with vital feedback during the creation of the APEX methodology. By experimenting with early versions of the program in existing Amgen facilities, the team was able to adjust and modify the tools and methods employed to fit within Amgen's culture. Admittedly, the fact that both facilities were not in production during the engagements was a less than ideal situation. However, if the group had waited for more 'ideal' opportunities, the sites would be less likely to be open to the engagements and the overall timeline for the creation of APEX would have been much longer with potentially less applicability to the network.

The LakeCentre engagement occurred roughly two to three months into the initial APEX design efforts. Through the activities at the site, the team gained valuable insights into the benefits of sharing information prior to the team's arrival, brief yet frequent meetings with the management team and the need for full alignment of the goals of the improvement team and those of the site. As mentioned previously, this engagement helped also to highlight the key analyses that will likely be a starting point for future APEX efforts, setting off efforts to make the execution of these analyses simpler and more standardized. The lessons learned from LakeCentre essentially drove the development of APEX for the next several months.

Activities at the Fremont site unfolded in a much more deliberate fashion, with the members of the APEX team obtaining preparatory information about the site's operation several weeks before the first week at the site. The actual engagement took place almost six months into the development of APEX, and as a result represented the first test instance of a fully developed methodology. The implementation of the lessons learned from LakeCentre helped to build the site management's confidence in the team's abilities and ultimately led to a very successful kick-off effort. While the APEX team was still encouraging feedback on the approach from those involved, the responses shifted from large-scale recommendations to minor innovations and improvements.

The testing of the APEX system during its development at the Amgen sites proved to be invaluable in the creation of the currently methodology. This approach of planning, executing and improving upon the APEX system will help to sustain improvement activities at Amgen, and ensure a continually improving continuous improvement system.

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# 6. Operational Change in a Changing Environment

During the development and implementation of the APEX initiative, large changes were occurring within Amgen as a whole that had a noticeable impact on the efforts of the team. These impacts were not necessarily all negative, but did require the adaptation of messaging, timelines for deployment and measures of success.

## *6.1. Organizational Changes and Dynamic Targets*

The most obvious change that was occurring during APEX development was the August announcement of plans to reduce the workforce by 12 – 14% and to reduce capital spending for 2008 by $1 billion.[40] This was the first time in the history of Amgen that a reduction in force would occur, and the effect on the employees was noticeable. As a result of the workforce reduction, roughly 700 eligible employees nationwide took voluntary separation packages and the company restructured many groups and divisions to better respond to the coming challenges.[41]

### 6.1.1. Application of Lean Principles amid Impending Staff Reductions

The biggest obstacle faced by the APEX implementation team as a result of the staff reductions at Amgen was attempting to apply lean principles in a time of great employment uncertainty. Given that general awareness of the APEX efforts came *after* the announcements of workforce reduction, it was difficult to arrive at a manufacturing site discussing process improvement and not to be viewed as looking for more places to reduce staff. Making the situation even more difficult, as mentioned previously, was the general perception by many employees that lean manufacturing meant removing labor from processes.

In order to combat these perceptions, the Operations Improvement team insisted on having meetings with management, supervisors and operators when beginning an APEX engagement to assure everyone of the intent of the efforts. Additionally, the team made sure to communicate

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[40] (Costello, 2007)

[41] (Chang, 2007)

the goals of APEX in improving daily operations at the site. To emphasize this further, the APEX team made a point of pursuing projects and improvements that were of particular importance to the operators as a starting point, demonstrating the value that Amgen places on their operators and their importance in all future process improvements.

### 6.1.2. Restructuring and Repositioning

During the restructuring activities at Amgen, the Operations Improvement team was also affected. First, the name of the group was changed from Corporate Manufacturing to Operations Improvement to reflect the focus and importance of its mission in the redesigned organization. The group also obtained some additional headcount from elsewhere in the organization to assist in the deployment efforts for APEX.

Another major development that occurred at this time was the repositioning of the group within the Operations division. Previously the team was a sub-team within Corporate Manufacturing, and had several layers of management between it and the senior management team of Amgen. Following the restructuring, the head of the newly dubbed Operations Improvement team was now a direct report to the head of Operations, merely one rung below the CEO of Amgen. This move reflected the high importance management placed on the APEX efforts for the future of the company and provided the team with a newfound source of buy-in and momentum to help drive continuous improvement efforts throughout the Operations division.

### 6.1.3. Shifting of Opportunity Areas and Potential Benefits

Amgen's decision to indefinitely postpone construction on a new manufacturing facility in Ireland,[42] along with the decreased demand for its Epogen and Aranesp products,[43] served to help shift the focus and potential benefits of the APEX initiative. Now that capital expenditures were limited within the company, the benefits of a continuous improvement system that could improve throughput or decrease operating costs from existing facilities had more apparent value. As a result, the progress of the APEX initiative became much more visible with the Operations

[42] (Amgen suspends Irish factory plans, 2007)

[43] (Costello, 2007)

division, with many executives hoping that the efforts of teams implementing the APEX methodology would result in further cost savings for the company.

## 6.2. Causal Loop Diagram of Forces Affecting Decisions within Amgen

Following the restructuring activities at Amgen and the initial efforts of the Operations Improvement team deploying APEX, several key forces affecting decisions with Amgen became apparent. While management at both the corporate and site levels were trying to facilitate the impending changes in operations, some of the actions taken ran counter to the continuous improvement principles that were being espoused by APEX. In order to capture these forces and the behavior that results, a simple causal loop diagram was created to illustrate the forces affecting decisions within the company (Figure 19).

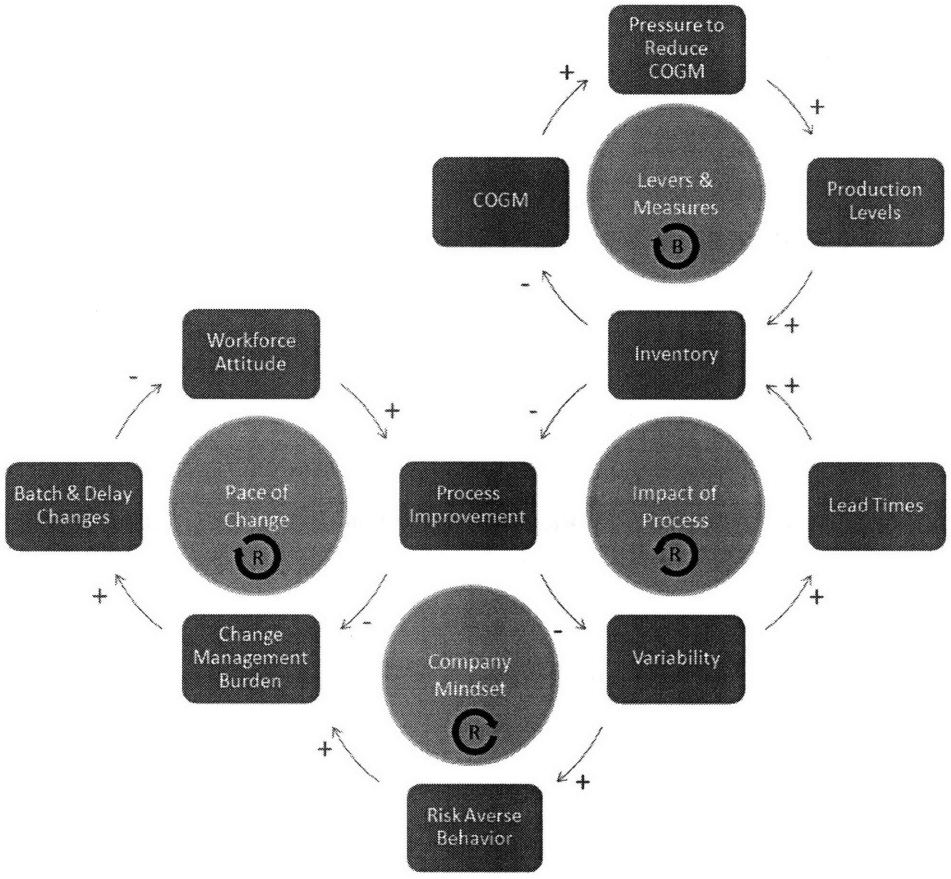


**Figure 19: Causal Loop Diagram of Forces within Amgen**

*Levers & Measures*

The first loop to discuss is the balancing *Levers & Measures* loop, which captures the main measures of success currently employed within Amgen and the levers that sites have to affect these measures. Sites are currently measured primarily on their cost of goods manufactured (COGM) as there is an understandable focus in Amgen currently on reducing costs. In addition, sites are also measure on lot success rates (how many lots that were started versus how many are successfully completed and released) and inventory availability (meeting stated minimums). Referring again to the causal loop diagram in Figure 19, as a site's COGM increases, there is increased pressure on that site to reduce COGM in the next period. In the current system, the only true lever that a site has to quickly reduce COGM is to increase production levels to spread out the site's fixed and variable costs over more lots. This in turn increases the inventory levels, which then help to reduce the COGM seen by corporate management. Since there is currently a focus only on inventory minimums, this encourages overproduction by the sites to compensate for increased costs. This excess inventory may later create problems for the company as a whole (storage costs, expiry, etc.), but the site has shown an ability to decrease COGM and will experience less pressure from senior management.

This loop demonstrates the main issue with using a cost accounting number such as COGM for the main driver of site performance. Cost accounting surely has a place within any company, but its usefulness does not extend beyond its stated purpose of accounting. As one Amgen employee proposed, cost accounting should be viewed in the same eye as validation. Validation occurs throughout regulated industries as a way to ensure that a stated process, test, cycle, or procedure performs as it was intended. While this is a necessary and useful step in the establishment of a process, it should not then drive *how* you do business. Instead, cost accounting (and validation) should be considered and addressed only after you have made the correct business (process) decision. This is in no way suggesting that these activities can be overlooked, rather that they should be used for their stated purpose and other measures should be used to evaluate business decisions. To address this issue, a concept for a new measure of plant performance based on improved productivity was developed (refer to 6.3).

*Impact of Process*

The second loop to discuss is the reinforcing *Impact of Process* loop, which captures the typical effects of inventory levels on process performance and vice versa. As was discussed in the *Levers & Measures* loop, inventory levels for many products at Amgen remain high to facilitate lower COGM. These high inventory levels have an impact on the manner in which the process is run, as an increased inventory leads to a decreased demand for process improvement. This occurs as there is no driver for increased efficiency if there is sufficient inventory to meet expected demand. In addition, the evaluation of site performance using lot success rates (mentioned above) also serves to discourage any experimentation with process improvement as the loss of a lot due to improvement activities, even with excess inventory, will reflect poorly in the site's metrics. With no focus on overall process improvement, variability is likely to increase, or at the very least remain constant. This increase in variability leads to an increase in overall lead time for the product, which reinforces the need for high inventory levels to meet customer demand. This is a dangerous loop to be caught in, which Amgen has recognized and resulted in the formation of the APEX methodology. However, by still focusing on COGM for site evaluation, the drivers for continuous improvement are outweighed by the measures of performance.

Arising from this loop is a large opportunity for Amgen to embrace and integrate a continuous improvement mindset that will outweigh other factors influencing site performance. An appropriate analogy to the idea of a continuous improvement culture is that of a compliance culture. Within the biopharmaceutical industry, the concept of a compliance culture is well known. Compliance in this sense encompasses adherence to GMP requirements, accountability for actions and consistently operating with the final patients in mind. As new employees are exposed and trained within the industry, their acceptance and understanding of compliance issues grows from aversion (a waste of time) to annoyance (a necessary evil) to acceptance (a manner to provide protection to patients). Compliance is not any single activity that is performed, but rather an approach and mindset that guides the business. The same can be said for encouraging a continuous improvement culture within Amgen. The initial roll-out of APEX will be met with resistance, and seen as another flavor of the month. However, as the entire staff is repeatedly exposed to these efforts, they will slowly begin to see that these improvement projects are not something that gets in the way of their jobs, but instead improves and encompasses their work.

In order to ensure that this occurs, Amgen as a whole needs to encourage and expect that continuous improvement efforts will occur and should be used as a measure of performance at the sites.

### *Pace of Change*

The next loop is the reinforcing *Pace of Change* loop, which relates directly to the level of process improvement activities discussed previously. Currently within Amgen the level of continuous process improvement is low, a level that APEX hopes to increase. However, in the current state this low level of activity can actually be seen to cause an increase in the burden associated with Change Management activities. This occurs due to the unfamiliarity of employees with small improvements to processing as well as the amount of work associated with the process variability that occurs when improvement activities are not prevalent. Due to the complexities and volume of changes required by the systems within Amgen, employees have increased the time to implement changes by combining ('batching') many changes into one change control document to be more 'efficient.' This reaction to paperwork intensive processes is very common in companies just starting continuous improvement efforts. However, as the delays associated with these changes increase, employee satisfaction and overall attitude tend to decrease. Employees begin to feel that the changes or improvements they propose are not appreciated, and the burden associated with their daily tasks becomes tiresome. This in turn leads to a decrease in employee participation in process improvement activities which then drives the cycle once again.

To address this loop and make it work for, rather than against, Amgen, the change management process needs to be investigated to see what improvements can be made to increase the pace of change. In general, most change control systems are built for compliance, not for speed, and can therefore become a road block for the rapid implementation of improvement efforts. However, in times of urgent need such as reaction to new requirements or a regulatory inspection, the process can be made to work more quickly. It is possible that this prioritization of changes could be mimicked to allow for quick execution of process improvements. Alternatively, a smaller system could be developed to handle these changes related to process improvements, with that system referring certain specific improvements to the standard change control system if it needs a full compliance review.

### *Company Mindset*

The final loop to discuss is the reinforcing *Company Mindset* loop, which describes the mindset of most companies in the regulated biopharmaceutical industry. This sub-loop helps to drive both the *Pace of Change* and *Impact of Process* loops through its interaction with variability and the level of change management burden. As the variability of any process increases, the level of risk-averse behavior increases as well. Risk-averse behavior can be interpreted as a direct analog to the common view of a compliance culture. As variability increases, it is the responsibility of the company to ensure that quality is maintained and patient safety is ensured. This increased aversion to any risk increases the hurdles associated with changing the process, driving the *Impact of Process* loop. In turn, the level of process improvement activities are reduced, further contributing to the levels of variability.

This risk-averse mindset is one of the most difficult obstacles to overcome in this industry as it is engrained in the attitudes of virtually all employees. In addressing this issue, the focus on patient safety and compliant operations can never be compromised. However, in order to facilitate continuous improvement throughout the company, this attitude must be addressed through education and experience. As employees begin to observe the benefits of continuous improvement on process performance, it is hoped that this will encourage further changes and improvements in the process. The main difficulty is then encouraging the initial improvement efforts, which can be achieved through effective management and a company-wide focus on improvement. Amgen is positioned well to encourage this behavior utilizing the APEX methodology, and as more employees are trained the desire for more improvements is expected to increase rapidly.

### *Summary of the Causal Loops*

It is very important to note here that while the behaviors described appear to be negative, three of the four loops identified are all *reinforcing* loops. Due to their reinforcing nature, these loops can help Amgen to drive its process improvement efforts once the initial state of process improvement is reversed. This is the current focus of the Operations Improvement team and the APEX methodology. As shown in the causal loops demonstrate, as process improvement activities are increased, the pace of change will increase, the company mindset will improve, and

the processes will improve resulting in lower lead times and inventory. While these improvements can all be driven through the adoption of the APEX methodology, the team still needed help to address the levers and measures used within Operations

The importance of the forces affecting decisions within Amgen, while understood by many stakeholders at the site level, needed to be communicated to senior management. An earlier version of the causal loop diagram discussed above was created by the author to help summarize what measures, activities or cultural norms might be a hindrance to the continuous improvement efforts within Amgen. By demonstrating that the APEX methodology was facing obstacles due to the current levers and measures used to monitor the manufacturing sites, the Operations Improvement team was able to highlight the need for change. In response to this analysis and other factors, Amgen set about revising the metrics used to evaluate site performance.

## 6.3. Development of Variable Cost Productivity (VCP) Metric

The disconnect between the message delivered to sites to reduce costs and the way in which the sites were measured (using COGM) led to an effort to create a new metric that would fairly and accurately measure site performance from a financial standpoint. The head of the Operations Improvement team reached out to the LFM interns working at Amgen to help him in the development of the new Amgen metric of Variable Cost Productivity, or VCP.

### *Emphasis of VCP Metric*

The VCP metric was intended to emphasize the value added to products at each site, rather than the overall accounting charges that may result. While COGM and other overall measurements of performance are useful in some contexts, the goal for the new metric was to determine what aspects of the accounting statement were important for evaluating the productivity of the operations at a biopharmaceutical manufacturing site.

The key considerations for this metric are to identify the costs particular to the products being manufactured at the facility, not the residual costs of the facility itself. Biotech facilities have extremely high up-front costs that often result in depreciation charges on the accounting statements, but these charges have no direct impact on the efficient use of the assets involved. It is the effective usage of assets that should be the measure of site performance, not the initial investment. Overhead is another cost allocation commonly used to evaluate performance, but

this does not address the appropriate usage of human resources within the facility which would be much more valuable.

To truly assess the performance of the operations, the focus of the new metric should instead be fully on the value add functions at the site. Within biopharmaceutical manufacturing, the raw materials used and the labor content applied during the production and release processes encompass the vast majority of the added value at the site. Given that these factors are largely under site control, they are ideal for the evaluation of the productivity of a site's operations. By measuring the sites using a metric focused on these 'controllable' costs, the desired behavior of fostering continuous improvement should gain momentum.

***Background Work***

The LFM interns were told to begin from scratch in the development of this metric, knowing only that it must allow for the fair evaluation of site financial performance from year to year and that it should be calculated in a way that complements the new company focus on continuous improvement. To begin their work, the interns held several brainstorming sessions to develop potential metric ideas. The group also met with several key stakeholders in the finance organization to further develop their concepts and obtain access to the Amgen cost system to determine which items were currently utilized for site assessment using COGM.

Using these data, the team identified which cost elements were 'controllable' by the site and which were unavoidable costs as long as the site was in operation. As previously discussed, the cost of raw materials utilized in production was deemed controllable, as the site could reduce waste and improve the processes surrounding raw material handling to affect those costs. However, depreciation expenses and insurance costs were classified as unavoidable costs for which the site should not be held accountable. Any reductions or changes in those costs would be controlled at the corporate level, and should not be used to judge site performance. This analysis was completed by the team for all items listed, and the categorized list was then presented to the Operations Improvement and Finance teams for evaluation. Once the 'controllable' variable costs were agreed upon, the team could focus on developing the metric.

*Metric Development*

The concept behind the Variable Cost Productivity metric was loosely based on a similar metric used at General Electric, of which several Amgen employees have had exposure. Using this knowledge as a starting point, the LFM interns sought to create a calculation that was simple to execute, understand and implement. By using only the costs that the site controlled (variable costs), the metric results would be automatically more actionable for the site management teams. In order to develop the metric calculation, the team first needed to decide if the metric would be used to measure a site's performance against other sites, or simply against its own previous performance. Given that each site made different sets of products, even if some were common, it was very difficult to normalize the data to facilitate cross-site comparisons. For example, if one facility was producing a large dosage protein therapeutic (dosages in grams) and another was producing a small dosage product (dosages in milligrams), how could their costs be normalized by mass of product produced? In addition, issues arose when trying to compare facilities who manufactured drug substance, the protein itself, versus those who manufactured drug product, the final vials seen by the patients. To circumvent these issues and ensure the clarity of the metric calculation, it was decided and agreed upon with management that the metric would be used only to compare a single site's performance with its prior period performance. While this decision removed the ability to perform cross-site comparisons using the VCP metric, several other site metrics would still allow for comparisons throughout Operations. Also, while the numbers will not be directly comparable, sites can still discuss approaches to improving this metric during their regular operating reviews to share best practices throughout the company.

*VCP Metric Calculations*

The final calculations arrived at by the LFM team are deceptively simple yet very effective. There are no subtleties or nuances to the calculations, and the metric is simple to understand. First, using the agreed upon variable costs obtained from the Amgen cost system, the total variable costs for each site were captured. Most of the variable costs could be easily traced to a single product, but for multi-product facilities there are some joint costs that must be allocated. The final decisions regarding allocation of these types of costs will be determined by the finance department, but for the purposes of the development of the metric they were distributed evenly across products. Next, for each product produced at a site the final production volumes must be

provided in kilograms of protein product. Provided that this information is obtained for the last two years, this small amount of data is now sufficient to calculate the new metric.

As shown in Equation 2 below, only five basic calculations are required to compute the metric. First, the Variable Costs per kg for each product produced are calculated for the prior and current years. Next, there is an adjustment for any changes in product mix from year to year. The purpose of this adjustment is to ensure that a site is not judged based entirely on a demand change or a drop in scheduled production for a particular product. This adjustment results in a credit (decrease in production) or debit (increase in production) for the Variable Costs for that product. Using this combined information, the Adjusted Variable Costs can be calculated for every product. To determine the overall site performance with regard to this metric, simply sum the total adjusted variable costs and divide by the sum of the total units produced in the *prior* year. This provides an adjusted Variable Cost per kg that can be accurately compared year over year, and this final comparison is the source of the VCP metric. An example set of calculations are provided in Figure 20 for a two product site.

$$\textit{Product i Variable Cost per KG } \left(\$/_{kg}\right) = \frac{\textit{Total Variable Costs (\$)}}{\textit{Total Produced (kg)}}$$

$$\textit{Account for Mix} = -\Delta \textit{Total Variable Costs} \times \textit{Prior Year Variable Cost per KG}$$

$$\textit{Product i Adjusted Variable Cost per KG} = \frac{\textit{Current Year Total Variable Costs} + \textit{Account for Mix}}{\textit{Prior Year Total Produced}}$$

$$\textit{Site Adjusted Variable Cost per KG} = \frac{\sum_i \textit{Product i Adjusted Variable Cost per KG}}{\sum_i \textit{Prior Year Product i Total Produced}}$$

$$\textit{Y} - \textit{O} - \textit{Y Variable Cost Productivity (\%)} = \frac{\textit{Prior Year Site Variable Cost per KG} - \textit{Site Adjusted Variable Cost per KG}}{\textit{Prior Year Site Variable Cost per KG}}$$

**Equation 2: Variable Cost Productivity (VCP) Equations**

| | | 2006 | 2007 | Account for Mix | 2007 (2006 equivalent) |
|---|---|---|---|---|---|
| Product X | Total Variable Cost ($) | 300.00 | 200.00 | 150.00 | 350.00 |
| | Total Produced (kg) | 100.00 | 50.00 | | 100.00 |
| | **Variable Cost per KG ($/kg)** | **3.00** | **4.00** | | **3.50** |
| Product Y | Total Variable Cost ($) | 600.00 | 800.00 | (300.00) | 500.00 |
| | Total Produced (kg) | 50.00 | 75.00 | | 50.00 |
| | **Variable Cost per KG ($/kg)** | **12.00** | **10.67** | | **10.00** |
| Site | **Variable Cost per KG ($/kg)** | 6.00 | 8.00 | | 5.67 |
| | **Y-O-Y Variable Cost Productivity** | | | | **5.56%** |

**Figure 20: Example of Variable Cost Productivity Calculations**

***Implementation of VCP***

Following the development work for the metric, the final proposed design was presented to the management of the Operations Improvement group and ultimately the Finance group. These management teams liked the simplicity of the metric and recommended that it be included in a proposal to senior management, along with other proposed metrics, for improved metrics to be used throughout Amgen. The VCP metric was then endorsed by the senior leadership team at Amgen and is planned to be implemented and used at all sites beginning with the 2008 fiscal year.

# 7. Conclusions

## *7.1. Evaluation of Initial Lean Efforts at Amgen*

**Company and industry specific nomenclature is essential to make lean principles contextually relevant for the biopharmaceutical industry.** Through the creation of a training curriculum composed of real-life examples, a case study and a simulation exercise based on actual Amgen operations, the APEX team was able to present proven continuous improvement tools in a manner that was directly applicable to the issues that employees would be addressing. In addition, the Process Run-Rate Analysis tool developed by the author facilitated the application of the APEX tools by minimizing the up-front work required and demonstrating an understanding of the current production atmosphere within Amgen. Through the efforts of all involved with the APEX effort, it was demonstrated that lean and continuous improvement methods and tools are widely applicable in the biopharmaceutical industry.

**Relevant metrics are needed to facilitate multi-site alignment and drive the desired behavior.** The existing measures of site performance used by senior management, especially COGM, had a strong influence on the manufacturing sites and could result in decisions that would not align with the new focus on continuous improvement. To prevent conflicting messages and encourage improvement efforts, the Variable Cost Productivity metric was created to allow for a site focus on the accounting charges that were variable with regards to productivity. This new metric was standardized and adopted by all sites to foster alignment of goals with local decisions influencing site performance..

**Continuous improvement efforts can effectively leverage a science-based culture by applying it to a new business context.** Amgen had traditionally viewed its science-based culture in the context of drug development, process design and the analysis of technical issues within manufacturing. When creating the APEX methodology, the team stressed the foundation of continuous improvement in the scientific method to identify with and appeal to the culture within Amgen. This focus allowed for the team to expand the scope of the science-based culture

to include the improvement of business processes. This reliance on the existing culture for the deployment of APEX is hoped to help drive Amgen's lean transformation going forward.

## 7.2. Future Opportunities for LFM Internships at Amgen

Now that the implementation of APEX is well underway, there are many opportunities for future LFM internships at Amgen. The Operations Improvement group currently has a new LFM intern taking over the job responsibilities held by the author previously. In this role, the new intern will support the team implementing APEX projects at Amgen's Fremont facility, continuing the work performed at the close of 2007.

In addition to working directly with the implementation of APEX within operations, there are also possibilities for LFM internships in other areas at Amgen. One potential project could involve the analysis of manufacturing capability and capacity for the entire Amgen network. This project is finite in scope but still quite challenging and would require visits to all of Amgen's sites to determine the true capabilities and capacities of each facility. This information would be valuable for Amgen when considering where to produce its products in the future to efficiently balance the network.

Another potential project for an LFM would be to perform an end-to-end evaluation of the entire supply chain for a specific product. In performing this task, the intern could capture the actual performance of each step in the supply chain, determine the true overall lead times for products and help to identify the areas most in need of process improvement. This project could combine supply chain theory along with several APEX tools to help Amgen direct its resources for the best possible improvements in performance.

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## Appendix A – Amgen Case Study for Use in APEX Training (redacted)

During the spring of 2007, a large and highly profitable biotech company had a "good problem" on its hands. Due to the explosive growth of its blockbuster drug Wondergen, the newly constructed dedicated production facility was straining to produce enough material to meet demand. The demand for Wondergen was forecasted to continue growing (see Exhibit 1) and peak in 20[redacted], so the company had begun a large capital project to expand and effectively double the facility's purification capacity. Given that Wondergen is generated using a fermentation process, upstream capacity far exceeds that of purification capacity, leaving the single purification suite as the process bottleneck.

Luckily for manufacturing, the demand forecast was now fairly reliable. During the early years of Wondergen production, sales had far exceeded forecast by a large margin and created a real concern that further increases in demand could outstrip capacity. In response, the plant has been running around the clock for several years with 24/7 staffing. Purification cycle times[1] have been reduced to approximately 4 days and are running at a high success rate (see Exhibit 2), a major accomplishment for the plant. It is widely believed that a run rate[2] of 1.8 per week is as fast as the purification process could be run, which drove the decision to build an expansion area.

Based on the recent stabilization of forecast and an un-substantiated belief that production facilities at the company have significant "hidden capacity," a team was formed to work with the Wondergen production team to identify what opportunities may exist. You and your team arrive at the site and generate the data found in Exhibits 3 and 4 through interaction with area management, operators and subject matter experts. The Unit Operations in Exhibit 3 are presented in the order of the process, and each step occurs once in the execution of a run.

[1]Cycle time is defined as the total process time required to produce a single lot.

[2]Run Rate is defined as the frequency at which lots are initiated (or completed) for the product.

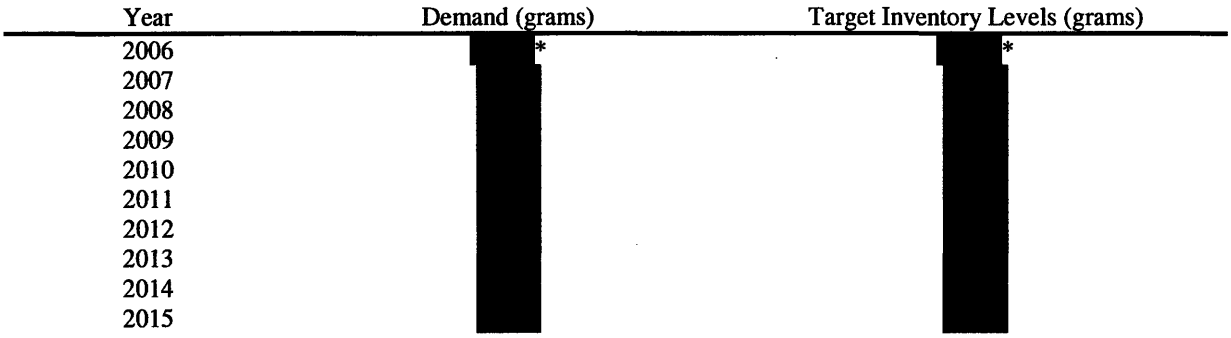
**Exercise**

Form groups of 3 – 4 and work together to answer the following questions about the Wondergen Case Study. You will have approximately 1.5 hours to read, analyze and report out your findings on the case. Use the flip charts and materials provided to summarize your main points to report out to the group when complete.

1. Create a high level process map for the Wondergen Purification Process detailing, at a minimum, the unit operations and the flow of product through the process.
2. Using data, calculations and the process map, identify
    a. The theoretical maximum process run rate (assume that multiple batches can be present in the suite and disregard support systems for this calculation)
    b. Unit operations or support systems that would become bottlenecks as you attempt to move from the current 4 day run rate to the theoretical maximum
    c. A "reasonable" run rate for the Wondergen Purification Process and the resulting production capacity (assume a [redacted]% success rate for this run rate)
3. Is the expansion project is required to meet the forecasted demand? If yes, how much additional capacity is needed? If no, why not?

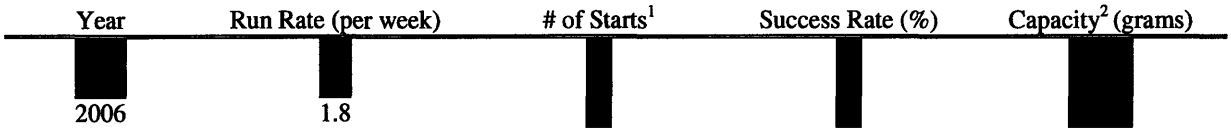
Following your analysis, your team will be reporting to site management on your findings. Identify the path forward you would recommend to management, based on your team's analysis, for production of Wondergen moving forward. Be sure to address all relevant questions and be prepared to back up your conclusions with data.

**Exhibit 1: Wondergen Demand and Inventory Forecast**




* Denotes Actual Values.

**Exhibit 2: Run Rates and Capacity of Wondergen Production Facility**




[1]Number of Starts based on Run Rate and an assumption of [redacted] weeks of production per year.
[2]Capacity based on average yield of [redacted] grams per Wondergen run.

**Exhibit 3: Wondergen Unit Operation Processing Times (in hours)**

| | Allotted Task Times (4 Day RR) | | | Theoretical Task Time | | |
|---|---|---|---|---|---|---|
| Unit Operation | Prep | Process | Post-Run | Prep | Process | Post-Run |
| Homogenization | 1 | 5 | 6 | 1 | 5 | 6 |
| Centrifugation | 3 | 15 | 3 | 2 | 15 | 3 |
| Oxidation | 1 | 20 | 4 | 1 | 19 | 4 |
| Depth Filtration | 3 | 4 | 4 | 3 | 3 | 4 |
| Chromatography 1 | 24 | 5 | 12 | 24 | 5 | 12 |
| Chromatography 2 | 9 | 8 | 6 | 8 | 5 | 5 |
| Chromatography 3 | 6 | 17 | 17 | 6 | 9 | 17 |
| UF/DF | 11 | 6 | 6 | 11 | 3 | 6 |
| Final Filtration | 2 | 3 | 4 | 2 | 3 | 4 |
| **Totals** | **60** | **83** | **62** | **58** | **67** | **61** |

Prep – all unit operation activities prior to the arrival of protein
Process – all unit operation activities that involve the protein
Post-Run – all unit operation activities that occur once the protein has moved on to the next unit operation

Source: Finite Schedule

**Exhibit 4: Support System Utilization per Wondergen Run**

| System | Units | Usage per Run | Availability per Day |
|---|---|---|---|
| WFI | Liters | 185000 | 71000 |
| PUR | Liters | 410000 | 205000 |
| Purification CIP | Cycles | 43 | 16 |
| Ferm/IB CIP | Cycles | 11 | 12 |
| Buffer Prep 1 | Buffer Batches | 6 | 3 |
| Buffer Prep 2 | Buffer Batches | 7 | 3 |
| Autoclave | Cycles | 13 | 12 |