A Network Planning Process and Inventory Strategy for High-Mix Low-Volume Markets

By Sally A. Smith

B.S. Mechanical Engineering, Washington University in St. Louis, 2006
M.S. Materials Science & Engineering, University of Arizona, 2009

SUBMITTED TO THE MIT SLOAN SCHOOL OF MANAGEMENT
AND THE ENGINEERING SYSTEMS DIVISION
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREES OF

MASTER OF BUSINESS ADMINISTRATION
AND
MASTER OF SCIENCE IN ENGINEERING SYSTEMS

IN CONJUNCTION WITH THE LEADERS FOR GLOBAL OPERATIONS PROGRAM AT THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY

JUNE 2012

Signature of Author _____
Engineering Systems Division, MIT Sloan School of Management
May 11, 2012

Certified by _____
Deborah Nightingale, Thesis Supervisor
Professor of the Practice, Aeronautics and Astronautics and Engineering Systems Division

Certified by _____
J. Bradley Morrison, Thesis Supervisor
Senior Lecturer, Engineering Systems Division

Read by _____
Donald Rosenfield, Thesis Reader
Senior Lecturer, MIT Sloan School of Management

Accepted by _____
Oli de Weck, Chair, Engineering Systems Education Committee
Associate Professor, Aeronautics and Astronautics and Engineering Systems Division

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

This page intentionally left blank.

A Network Planning Process and Inventory Strategy for High-Mix Low-Volume Markets

By Sally A. Smith

Submitted to the MIT Sloan School of Management and the Engineering Systems Division
on May 11, 2012 in Partial Fulfillment of the Requirements for the
Degrees of Master of Business Administration and Master of Science in Engineering Systems

Abstract

From June to December 2011, the impact of rapid international expansion on the Global Supply Chain organization at Amgen – one of the world's leading human therapeutics companies in the biotechnology industry – was investigated and a strategy was developed to mitigate the major challenges associated with globalization. Amgen is transitioning from predominantly high-volume low-mix manufacturing and a "one size fits all" Operations mentality; the company is challenged to not only now effectively and efficiently accommodate high-mix low-volume markets, but to also increase its overall market responsiveness and flexibility. To mitigate the challenges, an end-to-end depiction of a specific product's supply chain was developed and an inventory supermarket strategy supported by an Excel macro was developed. We believe the strategy mitigates the challenges, specifically by decreasing manufacturing lead time, buffering against supply chain variability, improving demand signaling and sustaining on-time deliveries. The Excel macro described in this thesis serves as a stepping-stone for the development of a future, more sustainable solution for Amgen's enterprise-wide systems.

Thesis Supervisor: Deborah Nightingale
Title: Professor of the Practice, Aeronautics and Astronautics and Engineering Systems Divisions

Thesis Supervisor: J. Bradley Morrison
Title: Senior Lecturer, Engineering Systems Division

Thesis Reader: Donald Rosenfield
Title: Senior Lecturer, MIT Sloan School of Management

This page intentionally left blank.

Acknowledgments

During my six-month internship engagement with Amgen, I was fortunate to have both an interesting and challenging topic to investigate, as well as an incredible network of peers, teammates and mentors. First, Eduardo Torres (Director, Supply Chain and internship supervisor) was an incredibly powerful force, maintaining purpose and value throughout the internship while also serving as an extraordinary mentor, further shaping my leadership beliefs and skills. Rayne Waller (VP, Global Supply Chain and internship sponsor) and Andrew Mica (Executive Director, Supply Chain) were enthusiastic and determined champions whose unwavering accessibility and support I so appreciated throughout the internship. The internship project would not have been nearly as successful without the brainpower, leadership and passion from my AML project teammates, including Esteban Santos (VP, AML Site Operations), Tomas Vicente (Executive Director, Supply Chain), Noemi Romero (Director, Finance), and – especially – Vivian Otero (Sr. Industrial Engineer) who spent countless hours patiently coaching and collaborating with me until the very end. I appreciate the guidance I received from Vishal Khanderia (Sr. Manager, Supply Chain) whose constant positive attitude and eagerness to learn were both contagious and inspiring. Chong-Im Kim (Sr. Specialist Production Planner) was instrumental in helping me gather data and understand the context of supply chain decisions, as well as in brainstorming feasible strategies to improve the organization and its processes. Lastly, some of my favorite working sessions occurred with the Business Center of Excellence employees responsible for planning systems including Tricia Darling and Fonz Perez.

Throughout the past two years, I've gained an incredible amount of perspective into both global manufacturing and operations, and into myself as a leader, team member and champion of manufacturing and operations. For these reasons and many more, I wish to acknowledge the Leaders for Global Operations (LGO) Program for its support of this work, as well as its support of me.

I am indebted to my MIT LGO peers – Marnix Hollander, Craig Rothman and Chris Garvin – who significantly bolstered my Microsoft Excel knowledge. While each had an internship project to execute, my three peers spent significant time sitting shoulder-to-shoulder with me to generously and patiently help improve the Excel macro used to demonstrate our inventory supermarket strategy. Furthermore, I don't know how she did it, but Leigh Hunnicutt (Sr. Manager, Plant Quality and LGO liaison) managed her full-time job while also ensuring the success of our internships and experiences – her expertise, mentorship and friendship truly made the experience a meaningful and memorable one.

I am incredibly appreciative for the support of my MIT advisors, Deborah Nightingale and J. Bradley Morrison, as well as the expertise of Professor Stephen Graves – each provided inspirational coaching and perspectives throughout and following the internship. Thank you, also, for reading my many thesis drafts!

Lastly, I am so grateful for the devoted support and encouragement I am lucky to always receive from Ian and my family. Thank you for always cheering me on.

This page intentionally left blank.

Table of Contents

List of Figures

1 Introduction

The information presented in this thesis is the result of an internship with Amgen, Inc. from June to December 2011. Amgen's Global Supply Chain organization sponsored the internship to investigate the impact of international expansion on its supply chain, and to outline some of the steps and resources required to optimize its planning systems to accommodate globalization. Two major challenges were identified as a result of market expansion, including the need for increased market responsiveness and the need for optimized manufacturing despite high-mix small-volume requirements from new, international markets.

Over the course of the six-month engagement, a cross-functional and cross-site team developed an end-to-end depiction of a specific product's supply chain, bringing to light a more thorough representation of Amgen's international expansion challenges. Furthermore, a pilot project strategy was developed that we believe mitigates the two major challenges resulting from international expansion.

1.1 Case for Change: Project Motivation

In an effort to increase its global footprint, Amgen aims to double the number of countries to which it supplies within the next three to five years. This international expansion brings additional operational challenges for Amgen, however, where "one size fits all" manufacturing and planning systems no longer support the future demand profile.

North American Commercial Operations (NACO) markets have historically driven focus on high-volume, low-mix production to serve countries like the US, which has high demand volumes and low variation in product concentrations, packaging, etc. With global expansion, however, today's product demand suggests two distinct market segments: while Amgen must continue serving its High-Volume, Low-Mix (HVLM) markets like the US, it must also support its newer High-Mix, Low-Volume (HMLV) customers[1] that have lower demand but increased SKU complexity due to drug concentration, packaging and other requirements. As Amgen increases its global footprint, these markets – classified as International Commercial Operations (ICO) markets – will increasingly contribute to product mix. Therefore, effectively managing market segmentation is critical to further improve efficiency and cost-effectiveness to best compete in the global marketplace.

To successfully execute in a global environment, the Global Supply Chain organization is faced with the challenge of adapting its current HVLM planning processes to serve HMLV markets. Going forward,

[1] Examples of High-Mix, Low-Volume (HMLV) markets include countries located in Europe, Latin America, Africa and Asia.

Global Supply Chain must effectively and creatively manage increased SKU complexity and increased low-volume demand to efficiently produce for and serve all its markets.

1.2 Hypothesis

The strategy described in this thesis addresses the two major HMLV challenges Amgen faces with international expansion:

1. Limited demand responsiveness due to a three month Fill / Finish manufacturing lead time
2. Increased changeover impact and scrap risk due to low-volume requirements

We believe the strategy presented in this thesis mitigates these two major challenges with the following results:

- Decreases Fill / Finish manufacturing lead time to approximately one month
- Provides a buffer against supply chain variability
- Improves demand signaling
- Sustains on-time deliveries

Throughout this thesis, the challenges faced by Amgen will be described, and the strategy aimed at mitigating these challenges will be detailed.

1.3 Research Methodology

The team followed the DMAIC Six Sigma Process Improvement methodology throughout the internship project, as shown in Figure 1. This methodology was selected because not only does it provide tools to target quality improvement initiatives, it also provides a methodology to improve business capabilities and processes (Yang and El-Haik). The approximate number of weeks spent at each stage during the internship is detailed in the figure, as well.

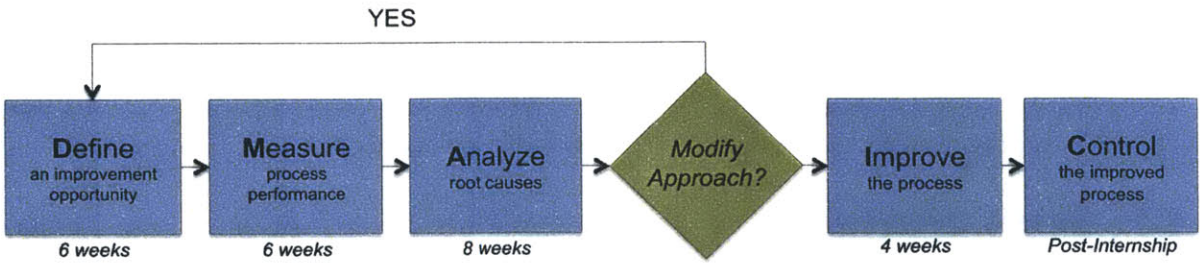


Figure 1 The Six Sigma Methodology DMAIC was followed throughout the project (Yang and El-Haik)

The project scope evolved significantly throughout the *Define* stage of the project, as an opportunity to engage multiple sites and functions arose that was not originally anticipated during the internship's creation. Throughout this stage, we shaped the business case, goals and objectives, and project scope, and also identified the roles responsibilities of each participant relative to the project (Yang and El-Haik). A significant amount of time was spent socializing the project with various leaders throughout the company to gain feedback and support.

The *Measure* and *Analyze* stages were often performed in parallel, or in a continuous loop-like fashion. One reason for this is that it wasn't always clear what needed to be measured (Yang and El-Haik). For instance, a value stream map (VSM) of a product's manufacturing process was created and defects that lengthen particular cycle times were identified, at which point targeted data was analyzed and added to the VSM to further enhance it. With additional information, the team was oftentimes able to drill further down into the defects, ultimately identifying the root causes. These two stages were many times difficult to execute, as Amgen is relatively new to systems like enterprise resource planning databases (such as SAP) and the source, quality and completeness of personal data files were at times unknown. As a result, we found the project was much more extensive than originally anticipated, and it was often necessary to loop all the way back to the *Define* stage to refine the scope and the required resources for the project.

A majority of the project involved developing an end-to-end snapshot of a particular product's supply chain to help Amgen's leadership and the Global Supply Chain organization understand the impact of globalization on its manufacturing and planning processes. This type of visibility was not previously available to the company. As a result, however, only about one month was spent in the *Improve* stage, or creating and documenting a strategy and tool to support planning processes as international expansion increases.

Prior to exiting the internship, all knowledge and documentation was transferred to two leads at Amgen's major manufacturing site, allowing them to continue the project and the *Control* stage of the project, during which the team will analyze control charts to understand whether the system has improved and by how much (Yang and El-Haik). This stage involves adapting the strategy and tool developed in the *Improve* stage to something more sustainable and applicable to the other products in Amgen's portfolio.

1.4 Thesis Overview

In the next section, an overview of the biotechnology industry is provided, followed by an overview of Amgen from organizational, financial and product perspectives. Following, a high-level description of the biotechnology manufacturing process is given, and flow charts are provided to supplement the process

descriptions. A portion of the manufacturing process is then expanded upon to illustrate the specific processes the internship focused on.

In Section 3, an organizational assessment of Amgen is presented. The Three Lens Analysis – a framework developed at MIT Sloan to aid in organizational evaluation – is used to analyze the company and the internship's home organization, Global Supply Chain, from strategic, political and cultural perspectives. The section concludes with a description of the internship project governance, as well as a portrayal of how the internship work was performed in collaboration with a cross-function and cross-network team.

In Section 4, the motivation behind the internship project is described by investigating Amgen's current supply chain in terms of volume and mix. A need for market and product segmentation is introduced.

In Section 5, a literature review and background information relating to the internship project is offered. Strategies and frameworks to mitigate challenges related to high-mix low-volume manufacturing are looked at from both a manufacturing and a planning perspective. Additionally, the concept of changeover impact is discussed and offered as a means for high-mix low-volume decision-making. The chapter concludes with an overview of inventory supermarkets and past work related to this strategy, thus setting the stage for the strategy executed during the internship.

In Section 6, an analysis of the current state of Amgen's expanding and changing supply chain is given. Two major challenges related to high-mix low-volume manufacturing are identified, and various constraints affecting any implemented supply chain strategy are described.

In Section 7, the process used to select an appropriate product to execute a pilot project future state vision is described. Ultimately, Product A was selected, and various product-specific characteristics are reviewed, including SKU complexity, its demand profile and testing requirements.

In Section 8, a future state vision to manage high-mix low-volume manufacturing from a planning perspective is presented. The strategy described was developed in collaboration with various functions across Amgen's broad global network, and serves as a short-term solution that demonstrates desired capabilities that should be implemented in a long-term, sustainable system-wide solution. The section concludes with a discussion of the pilot project deliverable's benefits, limitations and future enhancements.

In Section 9, conclusions of the research are offered, and recommendations for future work are made.

Lastly, in Section 10, the thesis is supplemented with a glossary of terms.

2 Industry and Business Background

The biotechnology industry – named in 1919 by Hungarian engineer Karl Ereky to describe the interaction between biology and human beings – began in the 1970s in Northern California. Founded shortly after in 1980, Amgen, Inc. was one of the first companies to capitalize on this science, pioneering the development of biotechnology medicines to serve patients. The industry has since spread worldwide to thousands of other companies and research institutions that engage in the many biotechnology sectors, such as healthcare, industry and environment, and biodefense (Amgen, Inc.).

This section will begin with an overview of the biotechnology industry, followed by a high-level introduction to Amgen and its products, financials and organizational structure. The section will conclude with a brief overview of the biotechnology manufacturing process.

2.1 Biotechnology Industry Overview

Unlike the pharmaceutical industry – which mainly manufactures synthesized drugs (e.g., aspirin) – the biotech industry manufactures biologics, or therapies based on the biology of living organisms. The industry is R&D-intensive and involves considerable cost and risk: bringing a new drug to market requires tremendous resources to the tune of $1B and 10-15 years, and merely one in every approximately 10 drugs ever makes it to market (Amgen, Inc.).

While the industry has changed significantly in a very short period of time due to successes in the biotech R&D arena, the industry's business model has experienced interesting and increasing challenges more recently. In the face of fiscal constraints[2], biosimilar threats and legislative focus on reforming healthcare[3], the industry is experiencing pressure to demonstrate value by reducing costs, increasing operating efficiency and pushing the innovation envelope, even despite historically high failure rates and complex regulatory requirements. Ernst & Young's *Beyond borders: Global biotechnology report 2011* eloquently and succinctly describes the challenges the biotech industry faces (Ernst & Young):

> *The [economic] crisis took a severe toll on funding (the model's key input) and placed innovation (its key output) under growing strain.*

Despite the changing environment, the biotechnology industry is expected to continue growing, primarily in the areas of cancer, infectious diseases and autoimmune therapies. It is believed that the demand on the

[2] Funding for R&D is highly dependent on national and private interests in the biotechnology industry (IBISWorld).

[3] The US healthcare reform bill passed by Congress in March 2010 aimed to increase patient access to biologics through biosimilars ("generics"), or approved biologic versions of biotech products post-patent expiry. The biosimilar sector is expected to subsequently grow, which will help decrease health care costs (Buzzard).

industry for decreased costs and increased productivity will drive competition to achieve in these areas (Silver).

2.2 Amgen Overview

Amgen, Inc. – originally called Applied Molecular Genetics – has grown from a start-up supported by $81,000 in seed money from each of its six venture capital investors into one of the world's leading human therapeutics companies in the biotechnology industry with $15B in revenue (2010) and 17,000 employees worldwide (Binder). Amgen's mission is simple: to serve patients, and it does so by discovering, developing, manufacturing and delivering innovative therapeutics at its sites shown in Figure 2 across the US, Puerto Rico and Europe.

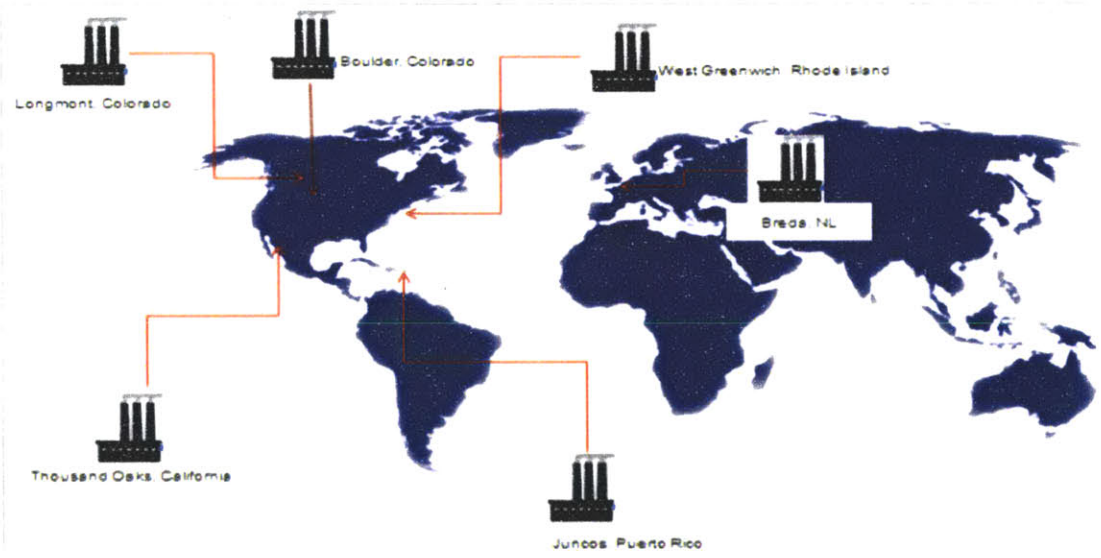


Figure 2 Amgen has manufacturing sites across the US, and in Puerto Rico and the Netherlands

Amgen's products – such as its early blockbusters Epogen® and Neupogen® – help patients fight a range of serious illnesses such as cancer, kidney disease, rheumatoid arthritis and bone disease (Amgen, Inc.). Headquartered in Thousand Oaks, CA, Amgen's products reach patients worldwide, with the majority of its sales currently concentrated in North America.

2.2.1 Products

Amgen has a product portfolio consisting of 10 products that target mainly the areas of oncology, hematology and inflammation. However, 90% of Amgen's sales are driven by just five, "blockbuster" drugs (LexisNexis): Neupogen® and Nuelasta® (treat infections in cancer patients); Enbrel® (treats rheumatoid arthritis); and Aranesp® and Epogen® (treat anemia). With the exception of Enbrel®, most of these core drugs are covered for patients by the government and / or the payer's healthcare plan. For this

reason, and since the company is one of the oldest biotech firms in the industry, Amgen is very vulnerable to biosimilars introduction as many of its core product patents are expiring near term (by 2015).

Patent expiry has in part been mitigated by the introduction of Sensipar®, a thyroid treatment and Amgen's first small molecule drug, which was launched in 2004. Several human monoclonal antibody drugs were also more recently introduced, including Amgen's first cancer drug, Vectibix® (colorectal cancer therapeutic); XGEVA® (treats bone disease); and Prolia® (treats osteoporosis). Prolia® - part of Amgen's denosomab franchise along with XGEVA®, which further diversifies the product portfolio - was expected to help offset the declining sales of Aranesp® and Epogen®, but in fact fell short of expectations following its 2010 launch.

While its portfolio is increasing in diversity with products like Sensipar® and the denosomab franchise, Amgen is actively working on filling its pipeline with other varied technology offerings. The commitment to filling this pipeline is evident in the 20% of revenues Amgen has invested in R&D over the last three years. The company continues to develop cancer, blood disease and inflammation therapeutics while also branching out into areas like cardiovascular disease and neuroscience. As of February 2011, the company claims to have 10 products in Phase 3 clinical trials, and a significant amount more in Phase 1 and Phase 2 (Amgen, Inc.).

2.2.2 Financials

With $15B in revenues – an increase of 2.81% over 2009 – Amgen's financial performance was considered sound in 2010 and has shown consistent growth year over year. The main driver of increased revenues was increased operating profits, which were a result of decreased costs (specifically, administrative costs) (OneSource). Amgen's financial accomplishments are perhaps a reflection of its increasing commitment to improving productivity to drive down costs.

2.2.3 Organizational Structure

Despite technically being a large, corporate company, Amgen still maintains a "start up" feel within its organizational structure and culture. From a high level, there are three main groups that make up Amgen's relatively tall organizational structure: R&D, Marketing and Operations. Despite there being a long path to the CEO, there is significant high-level visibility for an MIT LGO intern and high-level managers are accessible and knowledgeable about ground-level issues. To provide a perspective of the tall organizational structure, consider the following reporting line: the Director of Supply Chain Improvement reports to the Vice President of Global Supply Chain – who sponsored the internship – who reports to the Sr. Vice President of Manufacturing, who in turn reports to the Executive Vice President of Operations.

The Global Supply Chain organization went through significant organizational changes throughout the internship, aiming to better align its approximately 300-person team to support Amgen's new global expansion initiatives. The organization transitioned from somewhat site-based teams to more region-specific teams, and took on a modified function-based organizational structure. Within Global Supply Chain are various planning and distribution groups, as well as small "consulting-like" groups like Operations Strategic Planning (OSP) and Supply Chain Improvement which take on strategic operations projects that often times work across Amgen's network, both functionally and geographically.

The Supply Chain Improvement team directly supported the internship. This small group (3-5 people) aims to advance / evolve supply chain operations at the global, regional and site levels to support Amgen's global ambitions by partnering across the manufacturing network to leverage knowledge and manage transformation.

2.3 Biotechnology Process Overview

Manufacturing biologics – which are mainly proteins, or large molecules that are highly sensitive to environmental factors – is a complex process that involves strict process controls, long lead times on the order of years, and high costs of up to hundreds of millions of dollars. This thesis focuses primarily on a portion of the entire manufacturing process referred to as Fill / Finish. In the following sections, the entire manufacturing process will be explained at a high-level, and Fill / Finish will be elaborated upon in more detail in the following sections.

2.3.1 End-to-End Manufacturing and Scale-Up

The complex manufacturing and scale-up process can be summarized in the following four key steps, as shown in Figure 3: master cell line production; cell growth and protein production; protein isolation and purification; and product preparation for humans (Amgen, Inc.).

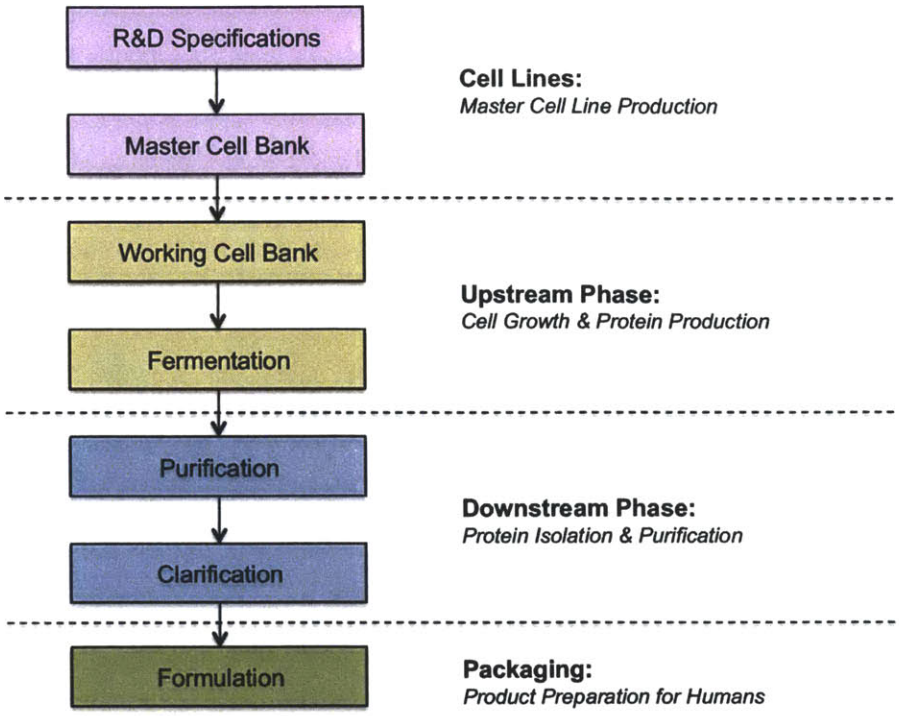


Figure 3 The manufacture of biologics can be summarized by the following four major steps: master cell line production; cell growth and protein production; protein isolation and purification; and product preparation for humans

The cell line production process begins with R&D specifications, which define the manufacturing methods and the drug's physical form (e.g., injection or infusion), which are then modified for large-scale production to meet market demands. A cell line for the therapeutic is then selected, which, for biologics, is usually derived from Chinese hamster ovary (CHO) cells, nonsecreting (NS0) cells or *E. coli* cell lines. These cell lines are used because they are generally regarded as safe (GRAS), synthesize proteins in a similar way that humans do, and are able to grow and produce product forever (Amgen, Inc.).

Once the cell line is created, it is cryopreserved. That is, scientists freeze a large quantity of vials containing the desired cells to create a cell bank. Cell banks are a two-tiered system, comprised of the master cell bank (MCB), a reserve of cells used by scientists only when absolutely necessary, and a working cell bank (WCB), which is derived from the MCB and is used to produce products during scale-up.

During the upstream phase, the protein product is produced using a vial of cryopreserved cells from the WCB, and is grown in a cell culture inside a flask containing a small volume of growth media (e.g., 5 mL). The growth media – a pH-specific mix of dry raw materials and water – facilitates cell growth (The Boston Globe). From this small volume, the protein product is scaled-up by transferring the constantly

growing and dividing cells into larger and larger growth vessels[4]. Given a favorable environment, this growth can and will continue forever. To ensure continuous fermentation, the environment is constantly monitored for acceptable characteristics like cell viability and product concentration. All in all, this upstream phase consumes approximately 32 – 40 days of production time.

In the downstream phase, the fermentation stage is followed by isolation and purification – which removes the desired protein product from the other cell components – and then by clarification, which removes the protein product from the remaining cellular debris. The still-crude product is then run through a series of chromatography steps to remove any remaining debris, allowing the product to reach approximately 99% purity. Before moving to the final steps, or Fill / Finish, the product is then diluted to the desired concentration (The Boston Globe). The downstream phase consumes approximately one week of production time, and the resulting output of this stage is drug substance (DS) or drug substance intermediate (DSI) contained in either carboys or cryovessels.

Once the protein product is isolated and purified, the product passes through the Fill / Finish manufacturing stages during which DS is formulated and presented per the R&D specifications for patient use (Amgen, Inc.).

2.3.2 Fill / Finish Manufacturing Stages

The Fill / Finish manufacturing stages encompass the manufacturing processes following the formulation manufacturing stage. As shown in Figure 4, product is taken from the final scale-up, drug substance stage, where product is stored in either large carboys or cryovessels, and transferred into a final presentation form, such as a vial or pre-filled syringe (PFS).

[4] Growth vessels vary in size, and can range from the initial flask (5 mL), to a bench top bioreactor (5 – 20 L), to a pilot scale bioreactor (50 – 200 L), and finally to production vessels (20,000 L or more).

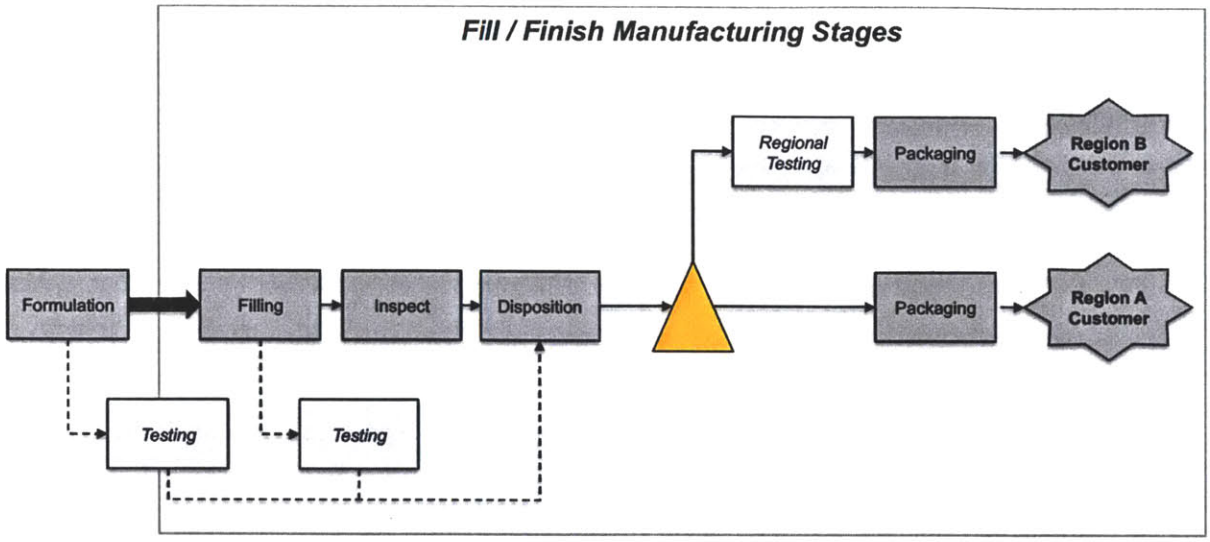


Figure 4 The Fill / Finish manufacturing stages include filling, in-line testing, inspection and packaging before the product is distributed to the customer

Throughout the formulation and filling stages, in-line tests are performed to ensure product compliance and quality. Test data is collected during the inspection stage, where quality engineers review the test results and "disposition" the product to either move it forward through the process, or hold it to perform continued testing and verification.

Following a successful disposition, product is held in a "nude," or unlabeled, form as inventory. Inventory is taken from this stage and either pushed downstream for packaging and distribution to the final customer, or is further tested in a specified country to pass region-specific requirements. During the packaging stage, nude vials or nude PFSs receive appropriate labels and paperwork per the customer specifications (e.g., labels and inserts are printed in specific languages per the final customer), and are then packaged in "packs," or a box containing anywhere from one to 30 vials or PFSs. Once packaged, product is distributed to the final customer, such as a country's distribution network or a healthcare provider.

3 Organizational Assessment

Realizing change in an organization is achieved through a challenging balance between the project's objectives and its various stakeholders. To accomplish the goals set out by the project team and its management, teams must constantly collaborate to understand and satisfy its stakeholders' needs. Throughout the internship, this balance was especially significant, as the project reached both team members and stakeholders across the Amgen network.

This section will begin with a Three Lens Analysis, or an assessment of Amgen as an organization from three different perspectives. The section will conclude with a description of the project governance and the roles and responsibilities of the team's members.

3.1 Three Lens Analysis

To provide insight into the environment at Amgen – specifically at its corporate headquarters in Thousand Oaks, CA – the organization is presented through three different lenses, or perspectives, which include the strategic, political and cultural lenses. This organizational evaluation focuses on the group most intimately involved with the internship, Global Supply Chain.

The strategic lens examines the company's organizational structure, specifically the way in which it's grouped, linked and aligned. An alternative view is gained through the political lens, which examines competition for power among stakeholders with various goals and interests within the organization. Lastly, the cultural lens provides insight by examining the organization within a historical context and analyzes how it functions per underlying assumptions (Carroll).

3.1.1 Strategic Analysis

From a high-level perspective, Research & Development, Operations, and Global Commercial Operations are the central groups at Amgen, which are supported by various functions spread across a broad, international geography. Under Operations sits Global Supply Chain. Teams are grouped by an activity, allowing employees to focus on specific tasks and goals and to develop specialized knowledge related to supply chain.

Figure 5 The Global Supply Chain organizational structure is group into three main categories including Supply Chain Architecture, Strategy and Risk and Systems

As shown in Figure 5, Global Supply Chain is comprised of three broad supply chain-related categories: Supply Chain Architecture, Strategy and Risk, and Systems. Structured teams are organized within these categories under the Global Supply Chain umbrella. Examples of teams are those such as North American and International Supply Chain, which manage product demand logistics; Operations Strategic Planning, which analyzes new optimization, equipment and other opportunities for Global Supply Chain; and Business and Projects, which is responsible for Amgen's Supply Chain systems and business processes. The Supply Chain Improvement team falls under the Global Supply Chain umbrella within the Strategy and Risk group, supporting its fellow Global Supply Chain teams' special projects while driving a network-level perspective throughout the organization.

The Global Supply Chain organization is substantial, and is currently in a state of growth and change, swelling from 100 to approximately 300 people by the end of the 2011. Despite this rapid expansion, communication throughout the large organization is handled well. For example, once a month, an all-staff meeting is held for Global Supply Chain leadership. These leaders then filter information through their respective teams via weekly staff meetings or email. Furthermore, while the VP Global Supply Chain holds quarterly all-staff meetings with the entire organization, he sits in the area with the rest of the group – he is a constant presence among his organization.

Supply Chain Improvement – the group managing the internship project – acts as a mini-consulting team for Global Supply Chain, and strives to think globally when designing solutions that best serve Amgen as a company. The team does this by fostering network-level thinking through open and inclusive working relationships, and by engaging key stakeholders at the global, site and regional levels when solving strategic problems. Because Amgen strives to become an increasingly more global company in the next three to five years, high priority is placed on collaborating with the entire network. Although small and in its infancy having just recently been established, the team and its leadership are well connected and

respected throughout the company – this link has helped the team access and disseminate information throughout the network.

3.1.2 Political Analysis

Amgen maintains a strong commitment to operating per its values, going so far as to withhold a promotion from someone strongly exhibiting all but one of its values, for example. Early on in its history, Amgen held a value that read: "Be Consensus-Driven." This value represented the company's commitment to making decisions only once consensus was achieved. While this is no longer an explicit, published value, the need to achieve consensus still seems to drive company behavior as highly-involved, data-driven discussions are often held to achieve agreement amongst multiple stakeholders.

As mentioned, Global Supply Chain is undergoing massive organizational changes to support the company's globalization strategy. Recently, a new Vice President position was created to help manage Amgen's expanding international supply chain, which will be followed by several other promotions, lateral shifts and team additions / rearrangements within the planned 300-person organization. The fluidity of the organizational structure, as well as opportunities for leadership positions, appears to affect the behavior of many employees. As described above, socializing information and gaining consensus amongst stakeholders is a common occurrence at Amgen. However, with the shifts in the organization, it appears sharing project direction and intentions are even more critical. Without commitments – or at least acceptance – from stakeholders, completing a successful project is extremely difficult. Support for efforts like proposed strategies or special projects is expected and monitored by leadership, which reinforces the same behavior in those lower in rank.

3.1.3 Cultural Analysis

A walk around Amgen's campus reveals the company places high importance on creating a top-quality, pristine environment – a priority that is also rigorously applied to its products. Amgen's HQs is situated in an affluent suburb of Los Angeles called Thousand Oaks that is, as the name suggests, lush with beautiful oak trees. Amgen's campus features similarly gorgeous, resort-worthy landscaping and one can spot beautiful cascading waterfalls from almost any vantage point, even in its 21,000 square foot fitness center. While it appears Amgen maintains a culture of spending top dollar on the work environment, this attitude is more recently waning in light of global competition.

Amgen employees are highly driven individuals who identify with high-performance teams and interesting, data-driven work. The spirit of collaboration between the workforce and the opportunity to perform challenging tasks appear to be the major elements Amgen employees identify with. The organization truly respects education and intellectual curiosity, yet also requires all employees to perform,

regardless of background. Furthermore, for the most part, employees are motivated to help one another and participate in new projects, even if it takes extra time. This is perhaps in part due to the "consensus-driven" need to understand everything that potentially affects one's work, but in general employees appear good-natured and gracious with personal time and effort.

Hard work and long hours seem to be a standard at Amgen HQs. However, employees also place a high priority on family time, seeking adventure outdoors and maintaining a healthy lifestyle. While these may seem nearly impossible to balance, employees are motivated to "work hard, play hard," a characteristic of the California lifestyle, in general.

3.2 Facilitating Change: Cross-Network Collaboration

The internship approached the problem statement in a very structured manner. Throughout the first month, project objectives and scope were defined with the core team and socialized with multiple stakeholders across the Amgen network. Over the course of the project, a defined, cross-network core team collaborated to develop the ultimate strategy.

3.2.1 Stakeholder Management

As previously mentioned, Amgen's retired value "Be Consensus-Driven" seems to still influence individuals' behavior across the company. Communicating project objectives, approaches and results is highly valued and sought out at Amgen. The importance of this behavior significantly influenced the first month of the internship, which was spent developing material to socialize the project with multiple stakeholders across the Amgen network. As shown in Figure 6, a project proposal was developed early on that clearly defined the goals, hypothesis, scope and key deliverables expected throughout the internship.

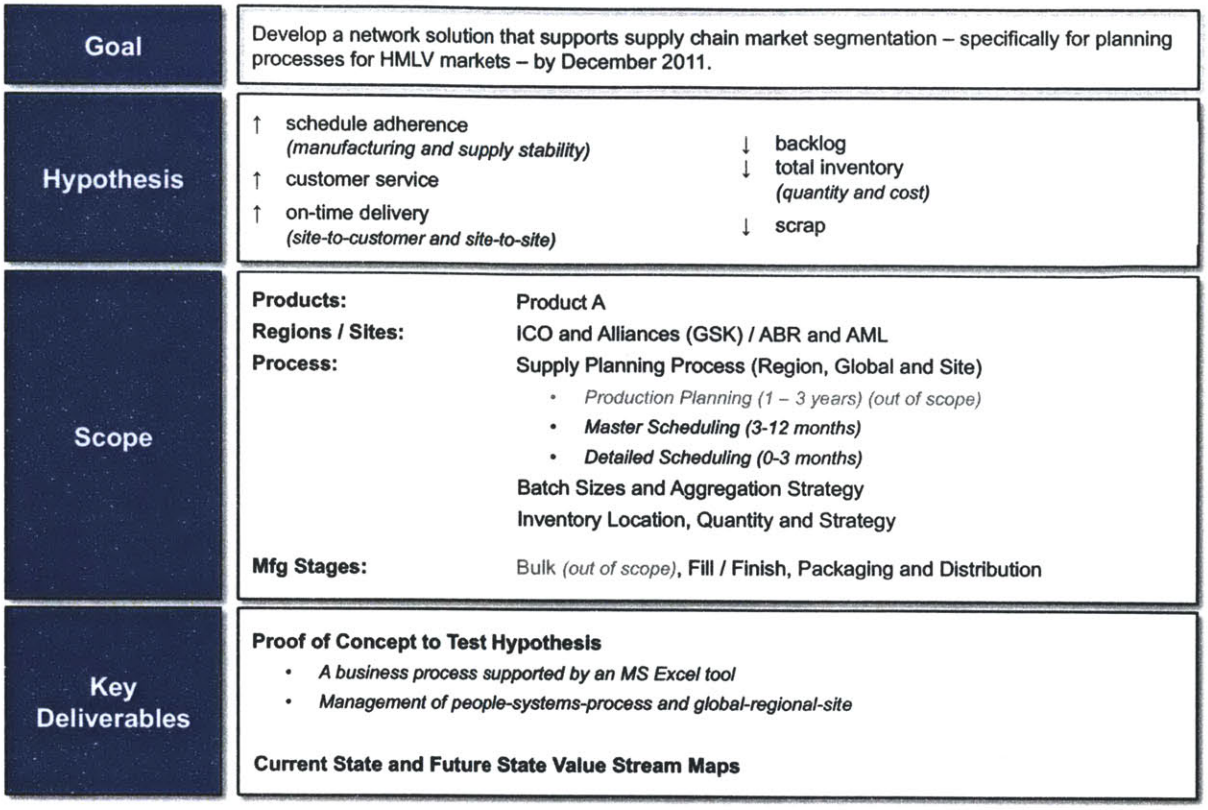


Figure 6 Snapshot of the project proposal PowerPoint developed with the internship core team and socialized with various stakeholders across the Amgen network

The project was initially socialized to a defined set of stakeholders who would be intimately involved with the internship. This initial group, or governance membership, shown in Figure 7, was comprised of leadership and peers holding a relationship with the project, whether they were future owners of the strategy or were simply expected to help facilitate success. Defining the governance membership and the related responsibilities upfront while socializing the project's intentions allowed for collection of powerful insight early on, and helped gain buy-in and support for the project going forward.

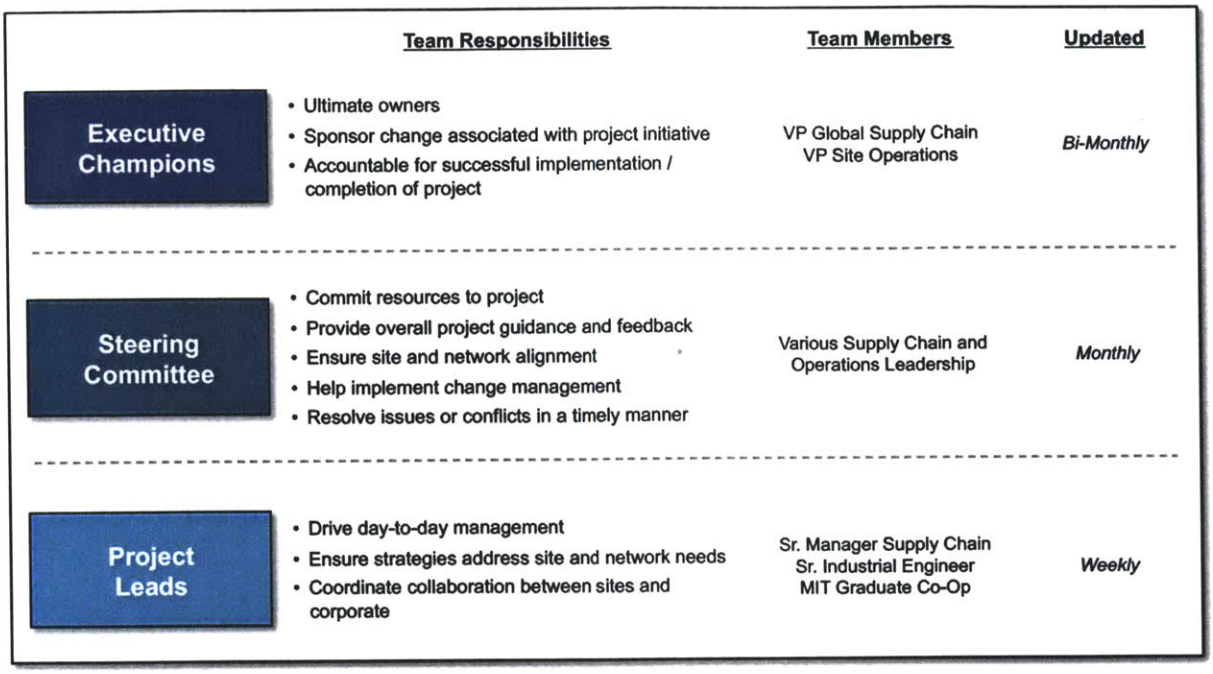


Figure 7 Snapshot of the governance membership PowerPoint used to define teams and enable input and timely decision making

At the core team level, a roles and responsibilities analysis called RACI – an acronym for the four levels of team membership: Responsible, Accountable, Consulted and Informed – was performed early in the project term. As shown in Figure 8, the RACI clearly defined each member's project responsibilities and defined who was accountable for various inputs into the project. These accountabilities were maintained throughout the project duration.

Project	Function	Role			
		R Responsible	A Accountable	C Consulted	I Informed
		Responsible for performing the work.	*Accountable for the final decision and has ultimate ownership.*	*Stays in the loop and is consulted prior to decision -making (two-way communication).*	*Informed about the work and decisions / follow-up actions (one-way communication).*
Product A	Global Supply Chain	Sr. Manager Supply Chain A MIT Graduate Co-Op	VP Global Supply Chain Director Supply Chain A	Sr. Planner Director Supply Chain E	
	Site 1 Supply Chain	Sr. Industrial Engineer	VP Site Operations Director Supply Chain B Director Supply Chain C		
	Site 2 Supply Chain	Sr. Manager Supply Chain B Director Supply Chain	Director Supply Chain D		
	International Quality		Director Quality A Director Quality B		

Figure 8 Snapshot of the RACI PowerPoint used to clarify project team responsibilities

Clearly defining project details like its goals, hypothesis, scope and key deliverables, as well as defining different stakeholders and their relative responsibilities, took significant time and effort. However, delivering a detailed plan to multiple stakeholders proved extremely valuable throughout the project, as a core group of important participants were fully aware and supportive of the internship efforts.

3.2.2 Core Team Governance

Within the first two weeks of the internship, the corporate-based team realized that another project with similar objectives and timeline was in works at Amgen's manufacturing site, AML. In response, the project core team re-formed as a combination of the corporate site, AML and an additional Amgen manufacturing site, ABR, which had valuable insight to contribute, as well. The sites gained an enhanced "network perspective" by collaborating with corporate representatives, and the corporate site gained valuable "hands-on" manufacturing insight from the site teams.

The newly combined team was at an immediate advantage in that its cross-site senior members were former site-based co-workers with excellent relationships who had successfully implemented site-level projects in the past. To acquaint other team members and to kick-off the project, the corporate team made a trip to the spearheading manufacturing site to work shoulder-to-shoulder with the Operations representatives for an entire week. This travel investment positively influenced the project in that the cross-network team members established good working relationships. This single week of close physical proximity not only increased the week's productivity; it also had lasting positive effects throughout the internship.

Throughout the project, the team was able to maintain its high level of productivity and collaboration by holding bi-weekly, cross-network and cross-functional team meetings over conference calls and webcasts. During these meetings, the teams reviewed data and strategies, gaining feedback from various Operations functions like Supply Chain Planning, Manufacturing Engineering and Quality. During the weeks without team meetings, the core team project leads remotely collaborated to gather and analyze data, and to develop various strategies that would be vetted during the large team meetings. To catalog information and ensure its availability to all team members, a web-based SharePoint site was established at Amgen.

While collaborating across three different time zones and three different Amgen sites was at times a challenge, the wide variety of perspectives and suggestions provided an invaluable advantage. The team was ultimately able to deliver a proposed strategy to Amgen's leadership that had already been examined and scrutinized by the entire networks and its various functional representatives.

4 Project Motivation: Demand Analytics and Segmentation

Preceding the internship start date, an analysis of Amgen's market demand was performed through a partnership between Mu Sigma, a consulting firm that helps companies institutionalize data-driven decision making (Mu Sigma), and Amgen's Supply Chain Improvement team. To better understand the impact of international expansion on Amgen Operations, the team analyzed both Amgen's global sales (actuals) over the three years from 2008 to 2010 and its projected sales (forecasts) for 2011 and 2012. This section will provide an analysis of qualitative data that supports market and product segmentation.

As shown in Figure 9, the analysis showed that Amgen's Region 1 has been – and will continue to be – a major contributor in terms of *unit* volume contribution. However, a shift in percent contribution has been observed over the last few years: Region 2 and Region 3 are increasingly contributing to both *pack* volume[5] and Stock-Keeping Unit (SKU[6]) count[7], which in turn introduces added operational complexity related to filling, packaging and distribution.

[5] "Packs" refer to s set of vials, a set of pre-filled syringes (PFSs), etc packaged together in a box along with the drug inserts, or paperwork (directions, warnings, etc). Packs exist in a variety of unit configurations. For instance, a "pack" could has two units (e.g., two vials) packaged together in a carton, or eight units (e.g., eight pre-filled syringes) packaged together in a carton, etc. The variety of configurations adds to supply chain complexity, as different markets prefer different configurations. Additionally, each configuration has a unique SKU that must be managed, further adding to supply chain complexity.

[6] Stock-Keeping Units, or SKUs, refer to a unique identifier (e.g., code, number, etc) that depicts a specific product for sale. For instance, a SKU may define a 5mL pre-filled syringe destined for Argentina, whereas a different SKU defines a 5mL pre-filled syringe destined for the US.

[7] Region 2 and Region 3 markets can also experience higher demand variability.

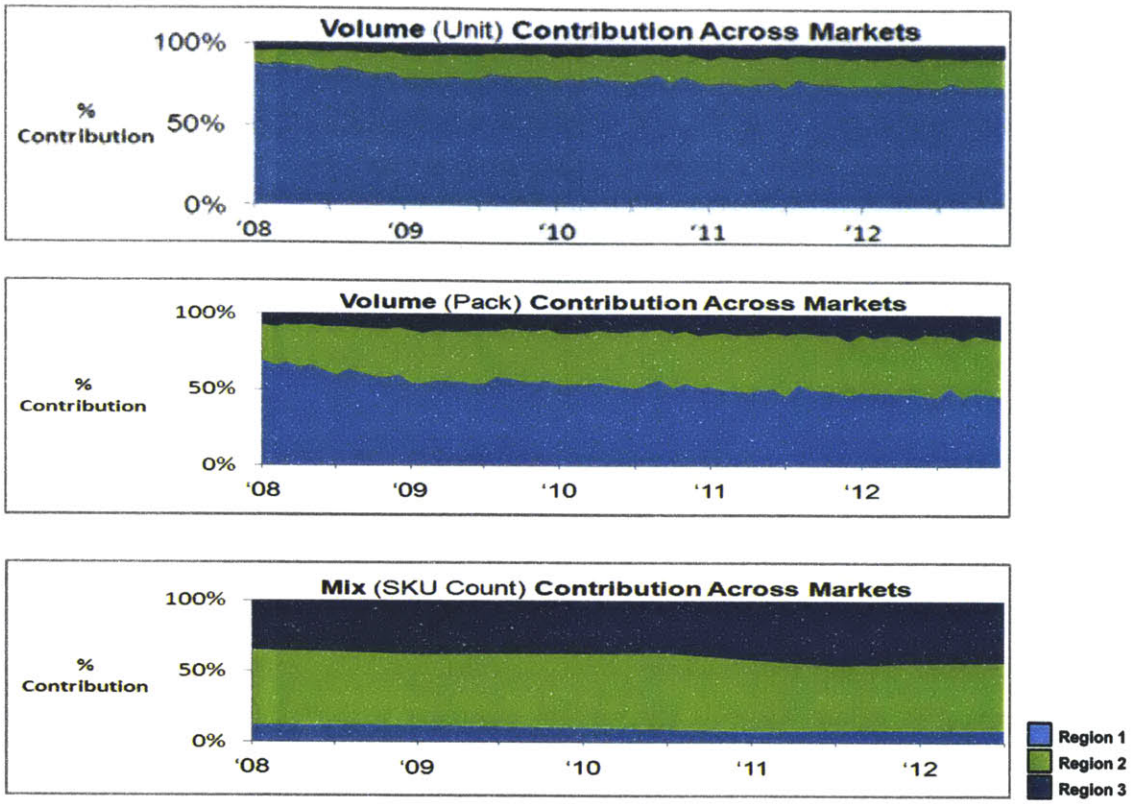


Figure 9 An analysis of Amgen's past global sales and projected sales shows that, while Region 1 is still the majority contributor in terms of unit volume, Region 2 and Region 3 are increasingly contributing to complexity both in terms of pack volume and SKU count

The analysis indicated that there is a clear segmentation evident in Amgen's market demand: on one hand, there is a stable, well-established market driven by large volumes but low complexity (e.g., Region 1) and on the other hand, there exists a growing market driven by smaller volumes, yet high complexity (Region 2 and Region 3). In other words, a High-Volume Low-Mix segment exists (e.g., Region 1) and a High-Mix Low-Volume segment exists (e.g., Region 2 and Region 3). This segmentation must be managed effectively to not only serve patients, but also to operate efficiently and effectively.

Segmentation is not confined to markets, however; the same behavior is evident on a product-level basis, as well. As shown in Figure 10, a case study of one of Amgen's products ("Product C") shows that some products exhibit High-Mix Low-Volume behavior (Region C) while others have High-Volume Low-Mix behavior (Regions A)[8]. This type of market segmentation is seen consistently across Amgen's products.

[8] The SKU mix boundary conditions shown in the segmentation graphs are merely estimates for illustrative purposed only. More analysis is required to better segment the SKU mix as high-mix versus low-mix.

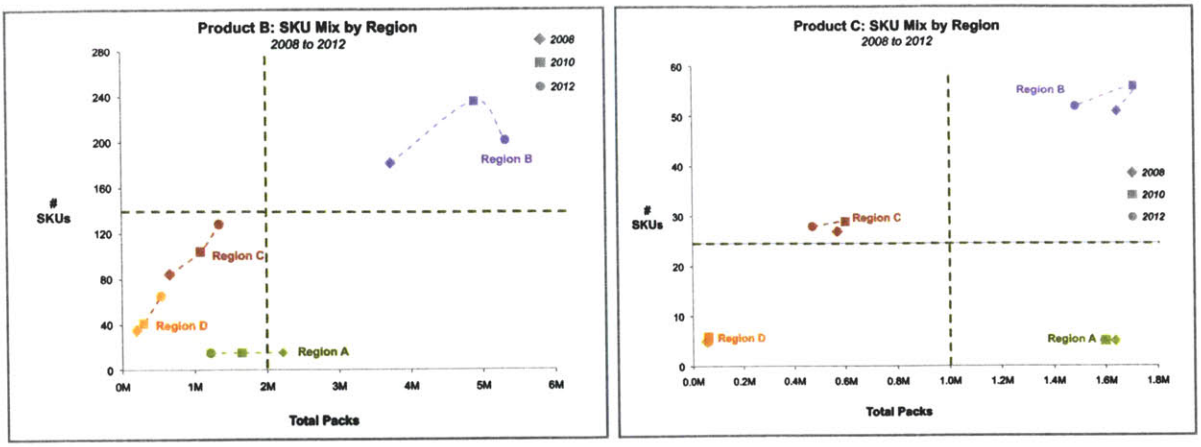


Figure 10 Segmentation is also evident at a product level, where some regions for both Product B and Product C exhibit high-mix behavior (Region B) and others exhibit low-mix behavior (Region A) while maintaining high volume demand

Further analysis of Product B's Region B is provided in Figure 11, which shows that a mere five countries drive 80% of demand; 10 different countries drive the remaining 20% of demand. While these 10 countries are critical to ensure Amgen's international expansion is successful, they further increase product mix and lead to manufacturing and planning inefficiencies.

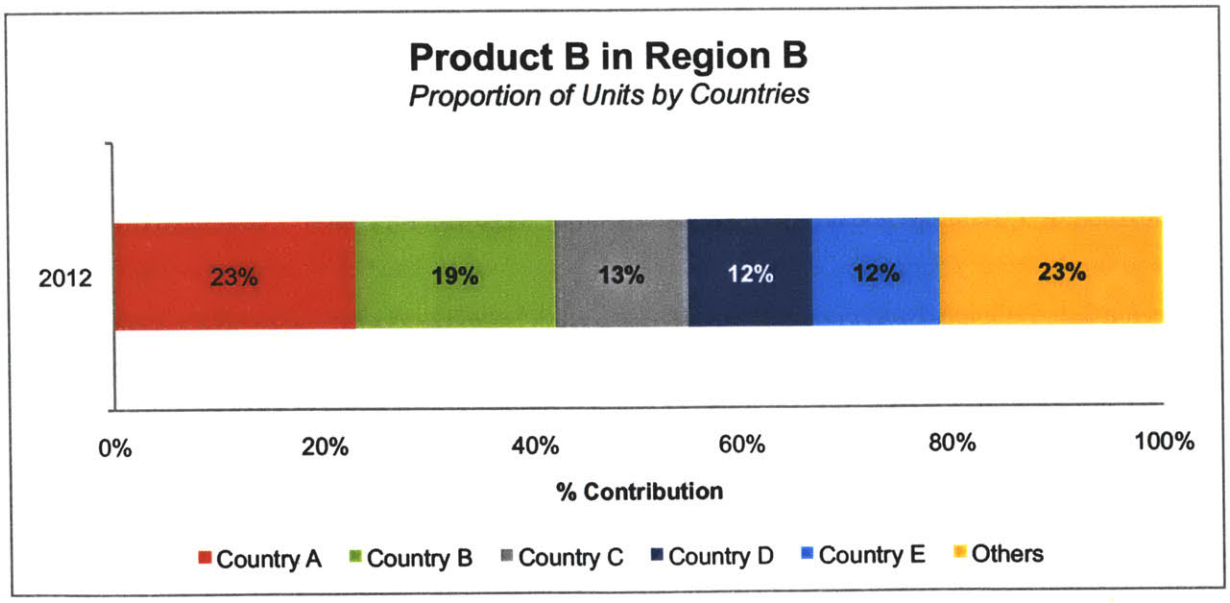


Figure 11 Five countries account for 80% of total Product B sales in Region B, while 10 countries drive the remaining 20% of demand

It is critical to understand the impact of market segmentation on Amgen's operating capabilities so that Amgen's manufacturing and planning systems can efficiently and effectively satisfy global demand. This concept isn't novel at Amgen, however; the significance of understanding market and product

segmentation was detailed by Ebel et. al in an analysis of pharmaceutical supply chains, urging the industry to investigate segmentation strategies in order to maintain quality and security, while improving supply chain speed and flexibility. From an operations perspective, the study found that not only does segmentation increase product availability with lower inventories; it has the added benefit of decreasing "firefighting" and last-minute changes within the manufacturing and supply chain organizations. From a cost perspective, the study found that segmentation results in lower overall costs due to reductions in scrap, overstocks and emergency transportation (Ebel, Großpietsch and Schrader).

The internship provided the first opportunity to perform a focused look at Amgen's segmentation opportunities and the corresponding impacts on its manufacturing and supply chain organizations and processes. While understanding segmentation and accommodating it appropriately with manufacturing and planning strategies is a newer concept to Amgen (as its demand was, until recently, relatively high-volume low-mix), this concept is commonplace in industries such as aerospace, semiconductor and food, for instance, as described in detail within the next section.

5 Literature Review

In his book, *High-Mix Low-Volume Manufacturing*, R. Michael Mahoney details groundbreaking work around the subject of high-mix low-volume manufacturing, describing strategies required to execute within this environment. Corporate strategists, he argues, often overlook high-mix low-volume manufacturing, while instead it must be uniquely designed and managed separate from other manufacturing systems such as high-volume manufacturing (Mahoney).

In this section, various manufacturing systems that vary per volume and mix are described followed by a discussion of how to optimize costs amid volume and mix tradeoffs. Next, the concept of changeover impact is introduced, followed by a discussion of various planning systems that support specific manufacturing environments. The section concludes with a discussion of batch sizing considerations, and an in-depth look at inventory supermarkets and their applications.

5.1 Manufacturing Systems

As mentioned in the previous section, Amgen is currently well equipped to efficiently satisfy high-volume demand from high-volume markets. However, since expansion into international markets introduces new customer dynamics for Amgen Operations, alternative, complementary manufacturing systems must be considered for low-volume environments. Currently, several of Amgen's manufacturing sites are investigating means to complement their existing high-volume manufacturing capabilities with solutions suitable for low-volume manufacturing. The following section is intended to provide a background of manufacturing systems, some of which may facilitate Amgen's accommodation of low-volume markets.

5.1.1 Manufacturing System Segmentation

A variety of manufacturing systems exist, ranging from low-volume, job shop-type production to sophisticated and highly efficient continuous flow operations, which is the type Amgen primarily utilizes today to satisfy what has largely been its high-volume, low-mix demand. Figure 12 depicts four types of mix and volume combinations a factory might experience[9]. This chart was used to understand how Amgen's manufacturing capabilities might evolve with its changing demand profile. Understanding the characteristics of demand will ultimately help Amgen complement its current highly automated manufacturing systems with a system well-suited for international markets' lower volume demand.

[9] As this concept is further studied at Amgen, the addition of a "low-to-medium volume" or "medium-to-high volume" segment may be appropriate to properly classify demand.

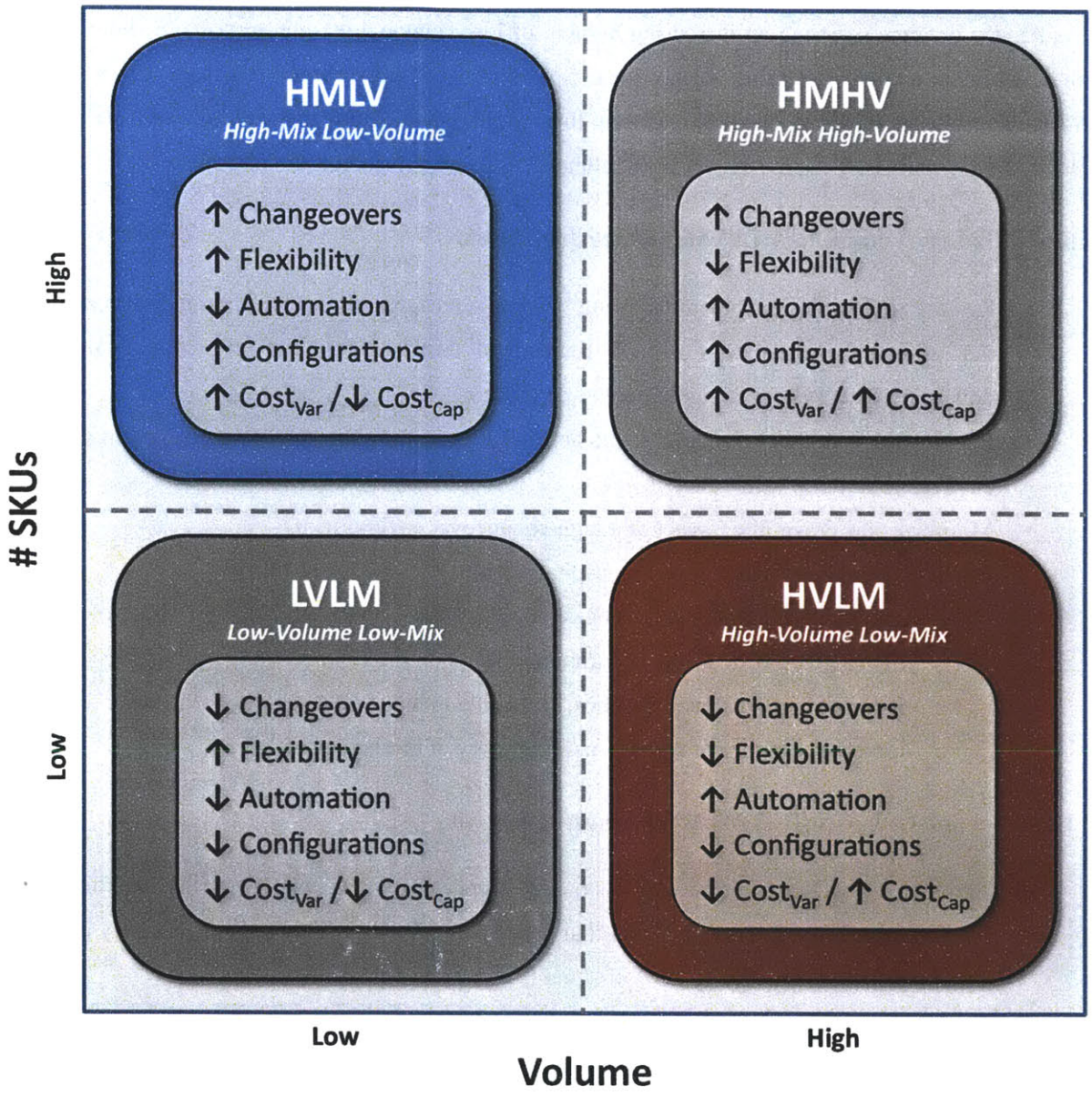


Figure 12 An appropriate manufacturing system can be designed according to demand profile(s), and can be classified by number of SKUs (high, low) and volume (high, low)

As previously mentioned, Amgen is currently well equipped to efficiently satisfy high-volume demand for high-volume markets – it is currently within the "HVLM quadrant." However, as the company expands internationally and into smaller markets with additional SKU requirements, it risks inching up into the "HMHV quadrant," which is an inefficient manufacturing space with frequent changeovers that constrain economies of scale.

As Amgen continues serving an increasing number of low-volume, high-mix markets, it should segment and optimize its manufacturing capabilities. Specifically, Amgen should maintain its high-volume manufacturing capabilities, but complement this with manufacturing capabilities suitable for more HMLV-type markets. The advantages and challenges of the two quadrants are listed below.

High-Mix Low-Volume (HMLV) Manufacturing System

- Requires a flexible, "cell manufacturing" system with a mix of manual labor and semi-automation that allows for alternate workflow routes and therefore potential protection from machine downtime. This system is highly people-dependent.
- Enables Economies of Scope[10], or the ability to lower the average cost / unit within a high-mix environment.
- Minimizes the downtime impact of a high-changeover environment.
- Provides flexibility[11] while lowering capital costs.
- HMLV manufacturing system challenges (Miltenburg):
    - Increased staffing levels and training to support multiple SKUs.
    - Increased product qualifications, especially to maintain flexibility.
    - Increased number of metrics and frequency of measurements[12].

High-Volume Low-Mix (HVLM) Manufacturing System

- Requires a highly automated, process-based, "continuous flow" manufacturing environment with little manual labor intervention and thus low operating costs. This system is highly equipment-dependent[13].
- Enables Economies of Scale by reducing the average cost / unit within a low-mix environment.
- Increased equipment utilization due to less changeovers and exploited machine efficiency.
- High capital costs amortized over large volumes.
- HVLM manufacturing system challenges (Miltenburg):
    - Equipment outages halt line(s) due to dedicated equipment design and thus limited flexibility.
    - High capital costs and footprint requirements.

---

[10] "Economies of Scope" refers to reducing the average cost for a firm when producing *two or more units*, whereas "Economies of Scale" refers to reducing average costs (cost / unit) by increasing the volume of a *single unit*.

[11] Flexibility refers to lines that can be easily re-configured to support a high product mix.

[12] Increased metrics are due to increased product mix.

[13] Given the high degree of equipment dependency, higher skilled staff (with correspondingly higher labor rates) is required to support the equipment (i.e., to perform technical maintenance, avoid excessive downtime, etc).

When considering implementing a new manufacturing system – or deciding how to best optimize an existing one – it is essential that these advantages and limitations are considered, along with the total cost.

5.1.2 Total Cost as a Function of Volume and Mix

One concept Mahoney discusses in *High-Mix Low-Volume Manufacturing* relates to a challenge Amgen currently faces: as mix is increasingly becoming a complexity factor with international expansion, it must be considered in tandem with volume when designing and optimizing manufacturing plans. Furthermore, he argues that companies must provide low-cost mix options and high responsiveness in order to differentiate themselves from the competition. To differentiate themselves, complexity costs must be minimized and be lower than the competition, which ultimately results in a flexible and agile manufacturing system. In his book, Mahoney details that the costs of managing increased mix – that is, managing additional inventory, material handling, setup, overhead, etc – increases 20-35% each time complexity is doubled. Taking advantage of economies of scale, or increases in production volume, which he states improves costs by 15-25% each time volume is double, can mitigate these costs (Mahoney).

The balance between volume- and mix-related manufacturing costs are conceptually detailed in Figure 13, which shows that as production volume and mix increase, total cost decreases until an optimal balance is achieved. This is the case only to a point, however.

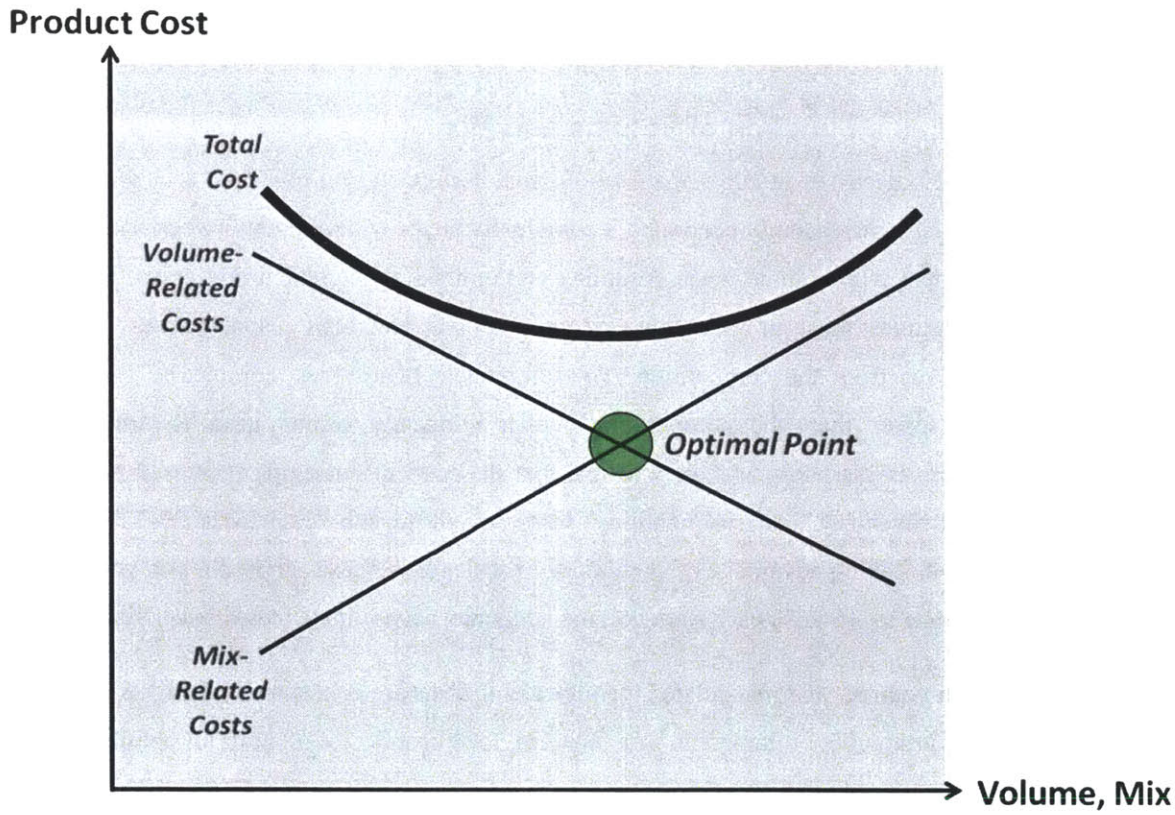


Figure 13 Economies of scale can be achieved by balancing product mix and cost (Mahoney)

Total costs again rise beyond the "optimal point" as product mix increases. This is the case even if volume is held constant (i.e., increasing mix increases costs regardless of volume). Producing more varied products on a single system, or manufacturing line, results in more frequent changeovers, which ultimately drives costs upward. It is for this reason that we recommend Amgen segment its demand per volume and mix, and implement production lines that are optimized and specialized based on these parameters.

As mentioned in the previous section, segmenting has its advantages and challenges; segmentation related to costs is no exception. For instance, while the HVLM category capitalizes on large volumes to deliver highly efficient, low variable cost products, it does so at the expense of flexibility and with high capital costs (e.g., expensive, highly automated equipment). On the other hand, the HMLV category thrives on flexibility and low capital costs, although this is done via higher variable costs (e.g., manual labor). While the cost / pack may in fact be higher for HMLV system (due to manual labor costs, for instance), the overall cost absorption of the plant may be better. In other words, the HVLM line may offset the higher

variable cost by achieving a lower cost / pack on the majority of its volume compared to costs incurred on HV machines.

5.1.3 Production System Design

In his book *Manufacturing Strategy: How to Formulate and Implement a Winning Plan*, Miltenburg outlines a systematic approach to identifying manufacturing needs and matching them to appropriate manufacturing strategies. Originally developed by Robert Hayes and Steven Wheelwright, an adapted representation of Miltenburg's Product / Volume-Layout / Flow (PV-LF) Matrix is shown in Figure 14. Only a handful of manufacturing systems exists, as shown in the figure, which Miltenburg feels has an important implication for manufacturing strategy (Miltenburg):

> *A focused factory should use the production system most able to produce the mix and volume of products and provide the manufacturing outputs required by the factory's customers.*

Per the matrix, each manufacturing system can further be classified according to a best-fit layout and material flow[14], as well as per product mix and volume, and offers managers a perspective on a best-fit manufacturing system. Currently, the majority of Amgen's packaging manufacturing falls into the category to the right of the dashed line in Figure 14, and is centered around the Equipment-Paced category, where highly-automated equipment intended for high-volume production is used to manufacture a variety of SKUs.

[14] The Job Shop manufacturing system may not be applicable in the BioPharma industry.

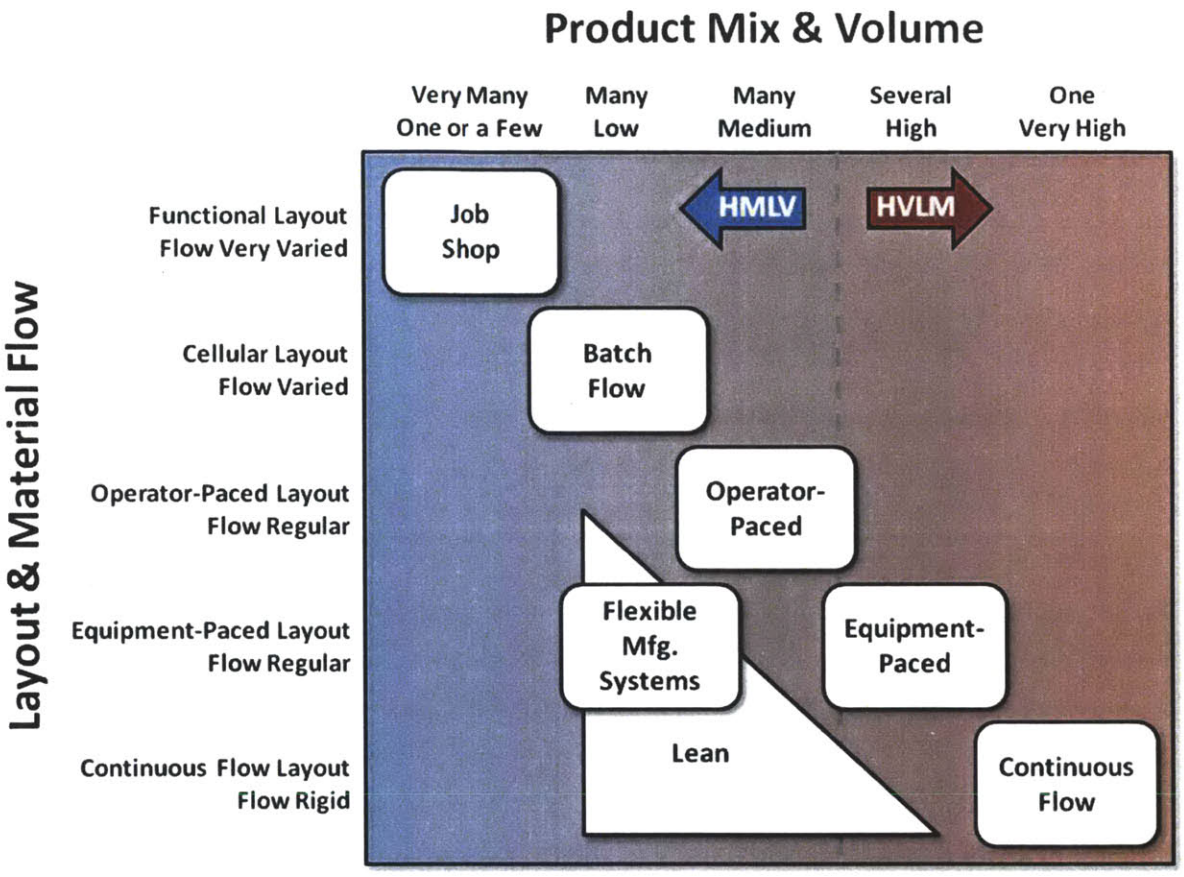


Figure 14 Manufacturing systems can be classified beyond simply mix and volume – the desired factory layout and material flow can also be a classifying factor (Miltenburg); Amgen packaging lines currently operate to the right of the dashed line, in the HVLM region, and more specifically can be classified as Equipment-Paced

The descriptions of each type of manufacturing system are listed below (Miltenburg).

Job Shop: Highly skilled workers run very small product volumes on workstations equipped with general purpose equipment.

Batch Flow: Slightly larger product volumes of less variety are run on modular workstations in batches / lots.

Operator-Paced Line: Even larger product volumes of less variety are run on workstations dedicated to product / a product family – the system is flexible and managed by operators.

Equipment-Paced Line: Similar to Operator-Paced, but this line produces at higher rates (although at the expense of flexibility).

Continuous Flow: One product is produced at very high volumes on highly automated equipment – little operator intervention is required, which results in low variable costs.

Lean: A collection of manufacturing principles typically applied to lines producing several products / product variations in medium to low volumes.

Flexible Manufacturing Systems: Capital-intensive, computer-controlled machines are linked by automated material delivery systems for low volume, process-based products – little or no operator intervention is required.

The company has an opportunity to assess its current manufacturing systems, segregate its demand and then determine best fit manufacturing systems for its new profile(s). If Amgen maintains solely a high-volume manufacturing system, yet continues running high-mix demand on its equipment, the company will find accommodating such a large spectrum of volumes ultimately affects its high-speed equipment utilization and productivity. Increased setups and closedowns due to small volume production consume valuable machine production time that is optimized for large volume runs. Transitioning HMLV products to an alternative manufacturing system will mitigate this efficiency loss.

The concept of segmenting products and focusing manufacturing by matching demand profiles with the appropriate manufacturing systems was heavily researched and well described by Wickham Skinner in his HBS article *The Focused Factory* (Skinner):

A factory that focuses on a narrow product mix for a particular market niche will outperform the conventional plant, which attempts a broader mission. Because its equipment, supporting systems, and procedures can concentrate on a limited task for one set of customers, its costs and especially its overhead are likely to be lower than those of a conventional plant.

5.1.4 Changeover Impact and Manufacturing System Design

The metric "Changeover Impact" as a function of total time for a given manufacturing line can be used to determine whether a lot or product type should be classified as HMLV or HVLM. Changeover Impact is defined as the ratio of changeover activities (such as setup and closedown time, or SUCD) compared to the total time (actual machine run time + SUCD time) that a product spends on a machine:

Equation 1 Changeover Impact

$$Impact_{Changeover} = \frac{time_{SUCD}}{time_{total}}$$

The concept of Changeover Impact is represented by Figure 15[15], which shows that productivity and machine utilization increase as the number of changeovers between lots is minimized. Minimizing changeovers allows a manufacturing system to approach an optimized state[16].

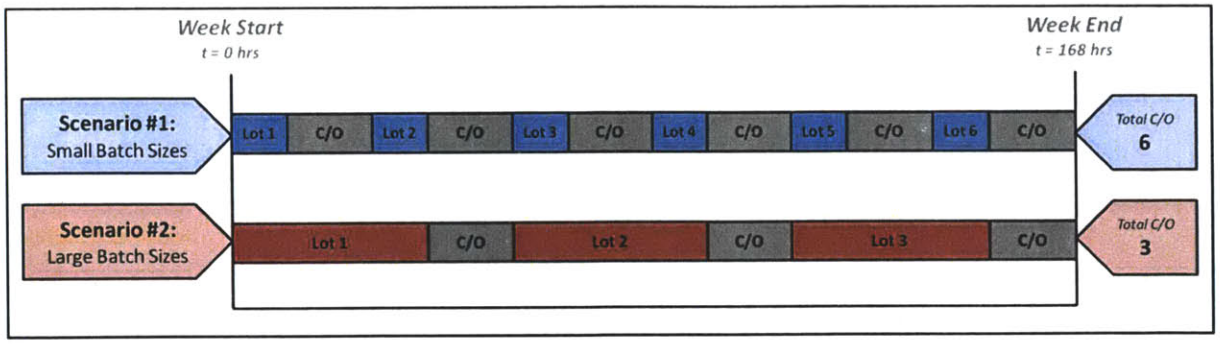


Figure 15 Conceptual illustration of changeover impact spread over a week of production time: when running small batch sizes, changeovers ("C/O") occur more frequently, whereas large batch sizes experience fewer changeovers

The adverse impact of small lots sizes and therefore an increased number of changeovers on capacity can be seen in Figure 16. Using data from one of Amgen's 2011 packaging lines, this graph demonstrates that as total production time for a lot decreases, the Changeover Impact increases and vice versa[17]. That is, a smaller lot that is run for a shorter amount of time leads to an increase in changeovers, which in turn increases Changeover Impact. This type of behavior is seen across all of Amgen's manufacturing sites.

The shaded region in the figure indicates an inflection point – which is packaging line-dependent and so may shift depending on various inputs such as equipment – that triggers a transition from requiring an HVLM to an HMLV manufacturing system. This type of plot and corresponding inflection point could therefore be used to indicate whether a particular customer's order is classified as HMLV or HVLM, and distinguish which line (HMLV or HVLM) would be most efficient to produce the product.

[15] The length of the each colored bar (e.g., "Lot 1") indicates the length of time required to run a certain batch size. That is, a shorter bar represents a smaller batch because it takes less time to run few units. Changeovers are assumed constant and independent of lot size.

[16] While Amgen continues to reduce changeovers through Operational Excellence activities, product segmentation (HVLM versus HMLV) must also be addressed to further achieve efficiency. Furthermore, minimizing changeovers and running larger batch sizes on high-speed equipment improves line performance by allowing the line to reach its rated potential.

[17] To develop the curve, Changeover Time (Setup Time + Closedown Time) was held constant, while Run Time was varied, as most changeovers at Amgen are relatively constant regardless of lot size (i.e., run time).

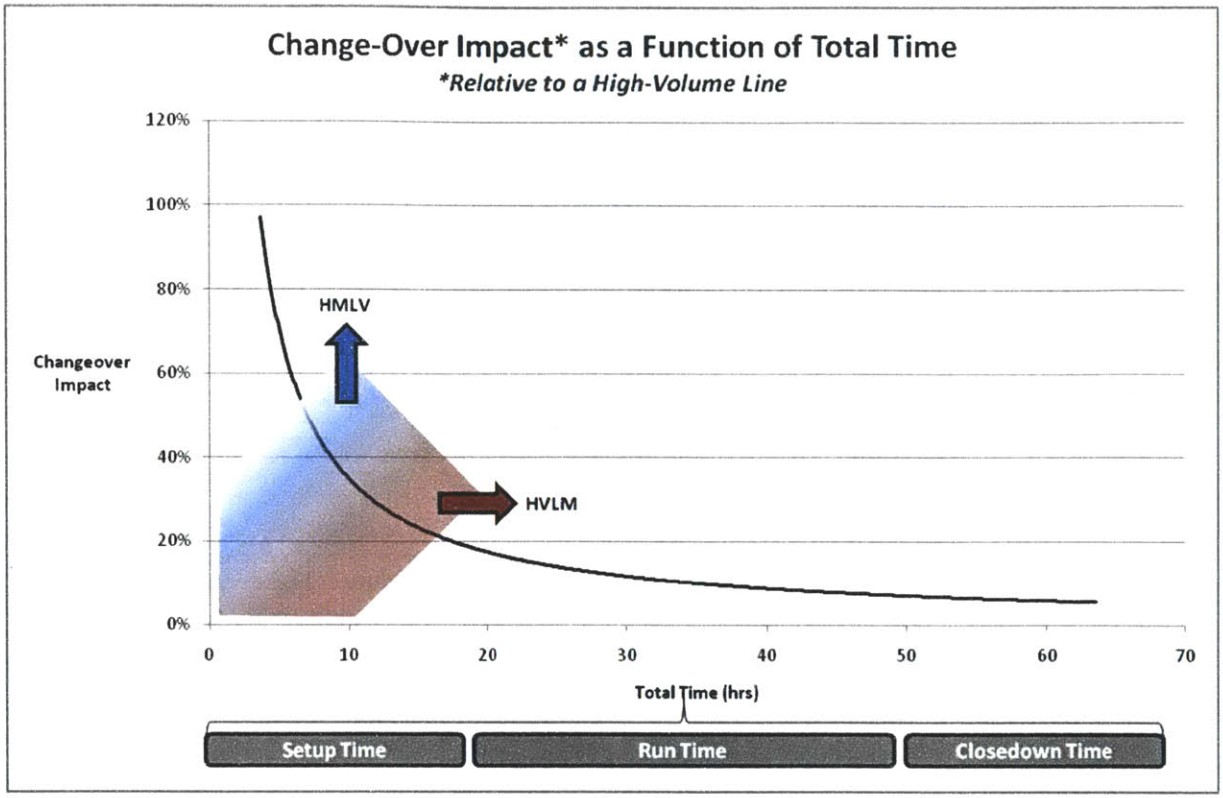


Figure 16 Changeover Impact increases as total time decreases (i.e., lot sizes decrease, thus decreasing run time); changeover time (setup + closedown time) was assumed constant, since this is the case for Amgen, regardless of lot size

The need for HMLV manufacturing capabilities is evident in Figure 17, a snapshot of an actual 2011 Amgen packaging line. Approximately one half of the lots forecast to be run on a packaging line are expected to have total times of one shift (eight hours) or less. In fact, 50% of these lots will take only four hours or less of total time. It is these lots that consume valuable machine time since changeovers must be performed between each short run time, low-volume lot.

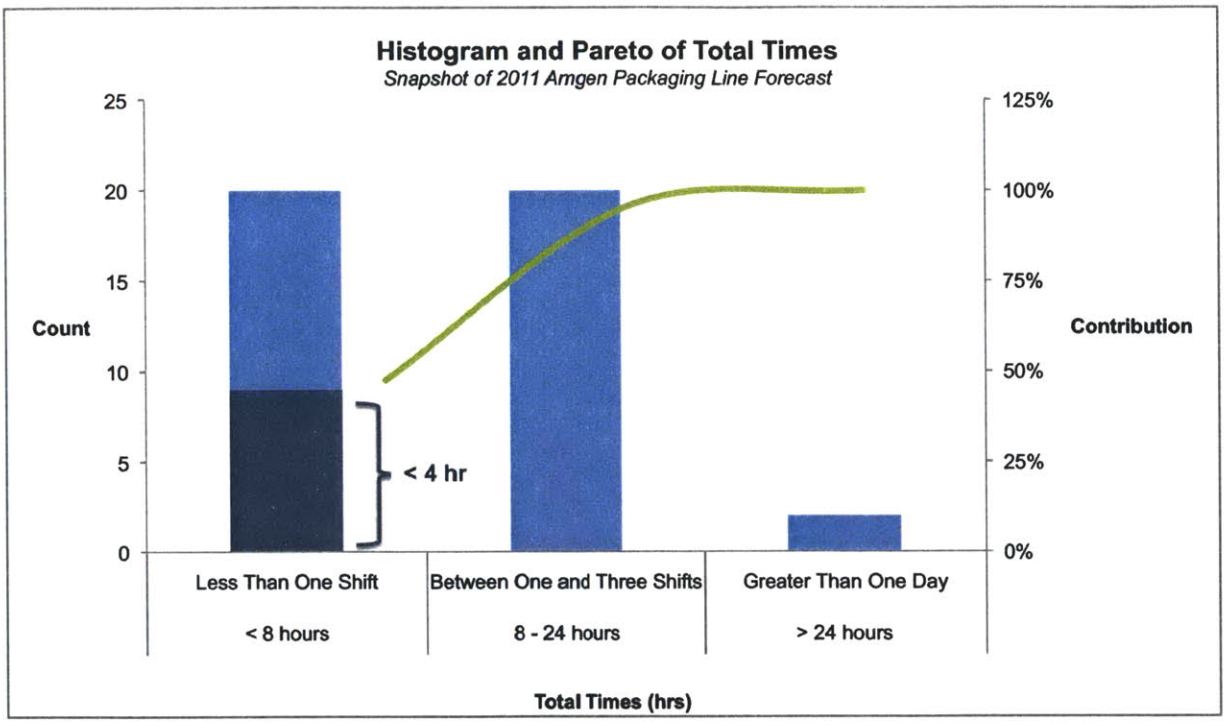


Figure 17 Histogram and pareto of total time spent running lots on a 2011 packaging line; half the lots run for less than eight hours, making them ideal candidates for a HMLV manufacturing system

This low-volume segment is expected to grow over the years as Amgen continues its international expansion; accordingly, mix will increase if the company continues entering and serving new markets in the same way it does today. Accommodating this segment with a HMLV solution will not only improve the cost of satisfying HMLV markets, but will allow the high-volume, high efficiency machines to work more efficiently.

5.2 Planning Systems

In order to successfully execute in a manufacturing and distribution environment, it's essential to have a planning system complementary to the manufacturing system. As with manufacturing systems, a variety of planning systems exist, ranging from fully forecast (i.e., "Push") or fully postponed (i.e., "Pull") manufacturing and distribution strategies, to a mix of forecast / postponement strategies.

5.2.1 Planning System Segmentation

As shown in Figure 18 adapted from Pagh and Cooper, planning systems can be organized by manufacturing (whether it's postponed or forecast) and distribution (whether it's postponed or forecast). Furthermore, Figure 19 outlines the various tradeoffs between each of the four planning systems. Descriptions of each of the planning systems follow the figures.

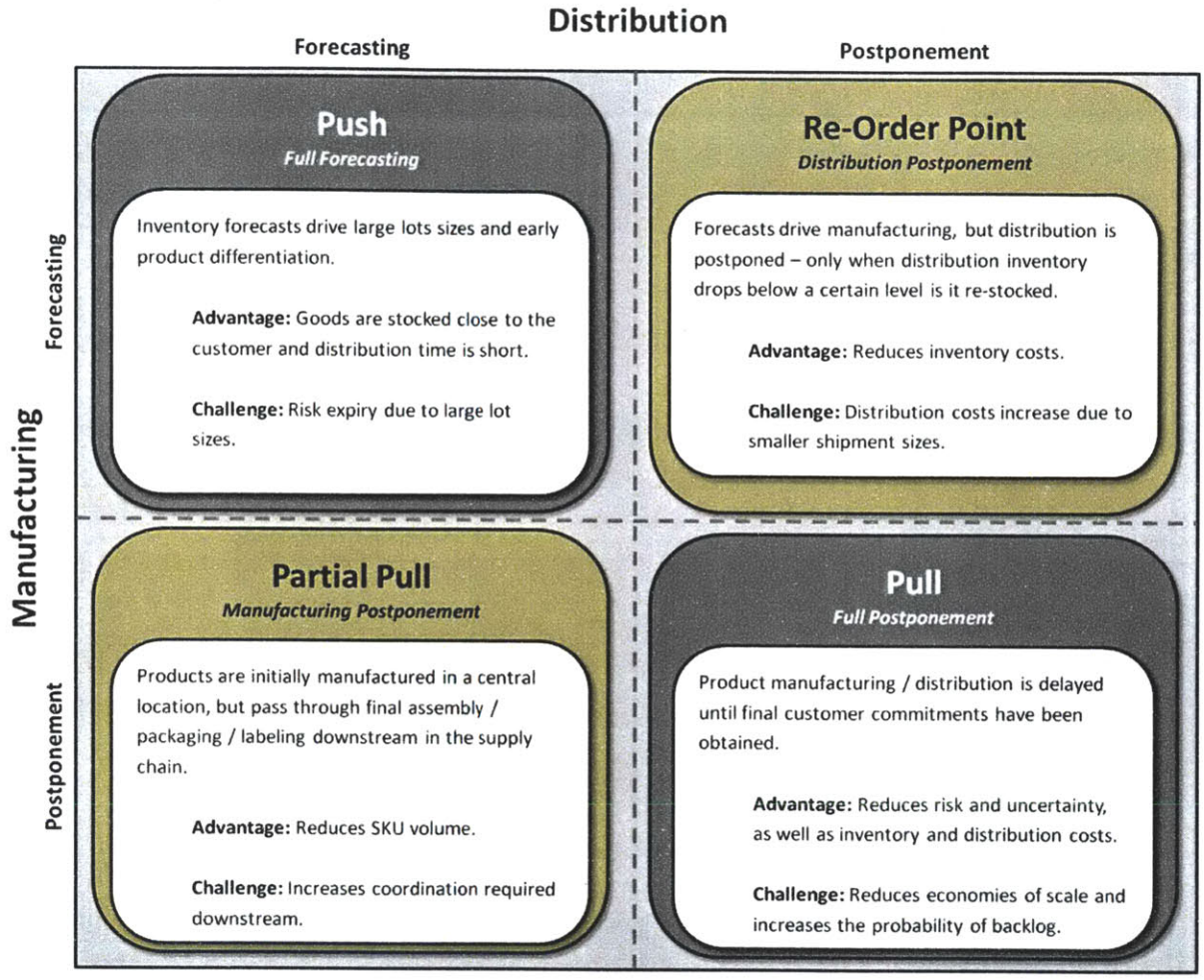


Figure 18 Planning systems can be categorized per manufacturing and distribution, and whether each of these categories are postponed or forecast; matrix adapted from Pagh and Cooper

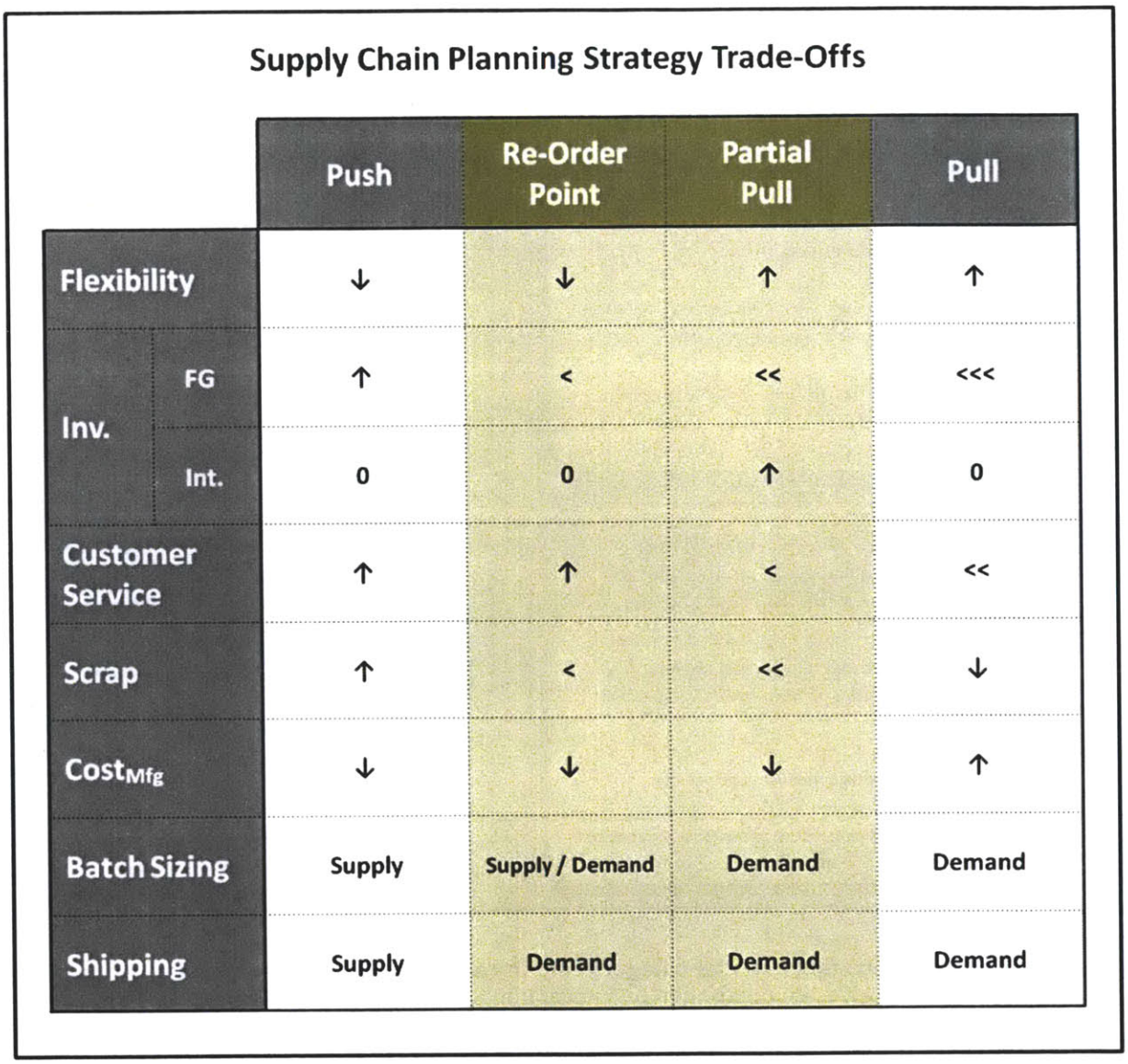


Figure 19 Various trade-offs between each of the four planning systems exist

Push (full forecasting): Based on inventory forecasts, Full Forecasting reduces stock-outs and supply chain costs – product differentiation is performed early, goods are held in inventory close to the customer and distribution time is short (Pagh and Cooper).

- Advantage:
    - Economies of scale are obtained through manufacturing and logistics – products are produced in large lot sizes.
- Challenges:
    - Obsolescence / expiry may result due to large lot production.
    - Increased inventory investment due to decentralized distribution centers.

Pull (full postponement): Full Postponement is the converse of Full Forecasting – this system reduces supply chain risk and uncertainty by delaying product manufacturing / distribution until final customer commitments have been obtained (Pagh and Cooper).

- Advantages:
    - Decreased manufacturing inventory costs.
    - Decreased distribution inventory.
- Challenges:
    - Reduced economies of scale, unless products are pre-built in the upstream manufacturing processes.

Re-Order Point (logistics postponement): Products are manufactured per a forecast, but distribution is postponed – completed products are directly distributed from a centralized warehouse to a final customer upon order commitment (Pagh and Cooper).

- Advantages:
    - Increased on-time deliveries of complete orders.
    - Decreased and improved reliability of lead-times.
    - Reduced inventory costs and reliance on forecasts.
    - Maintained manufacturing economies of scales.
- Challenge:
    - Increased distribution costs due to smaller shipment sizes / faster modes.

Partial Pull (manufacturing postponement): Products are initially manufactured in a centralized location, but pass through final assembly / packaging / labeling downstream in the supply chain only after (1) the products have been dispersed to different distribution centers and (2) customer commitments have been obtained (Pagh and Cooper).

- Advantages:
    - Reduced SKU volume and mix moved / stocked in anticipation of customer orders.
    - Simplified inventory planning and management, especially related to expiry.
    - Potential offloaded management of final assembly / packaging / labeling to a 3rd party.
- Challenges:
    - Reduced economies of scale at downstream operations (and thus increased costs).
    - Increased costs due to coordination with downstream supply chain management.

The power of planning systems rests in their applications to demand. Amgen has traditionally applied one planning system to the bulk of its very stable, high-volume low-mix demand: Push. However, today the company is finding that an additional planning system – Partial Pull – better accommodates its high-mix low-volume market segment. In their article *The value of flexibility: Pharma supply chain 2020*, Ebel et. al articulated the importance of applying a planning system well-suited for a specific type of demand, and that the success of the planning system depends on the planning process applied (Ebel, Großpietsch and Schrader):

> *Segmentation works only where segment-specific strategies are defined for all key processes, including forecasting and demand planning, service level and inventory management, production scheduling and capacity planning.*

Planning processes require robust procedures in order for them to be effectively executed, especially when more than one planning system is used to serve a range of markets, as is the case for Amgen.

5.2.2 Batch Size Planning

As discussed in Section 5.1.2: Total Cost as a Function of Volume and Mix, a balance between volume and mix must be considered, especially for high-mix low-volume manufacturing environments. Similarly, for Amgen's case, the balance between demand-supply variability and expiry / remaining shelf life must be considered when planning batch sizes for manufacturing.

As shown in Figure 20, a "sweet spot" – or optimal point – between large and small batch sizes exists. While producing large batch sizes is effective in terms of maximizing manufacturing capacity and

achieving economies of scale, it risks product scrap and expiry if market demand changes (both in volume and timing, as expiry is a concern). On the other hand, while small batch sizes minimize the risk for product scrap and maximize shelf life, it risks starving the market and potentially causing market share loss.

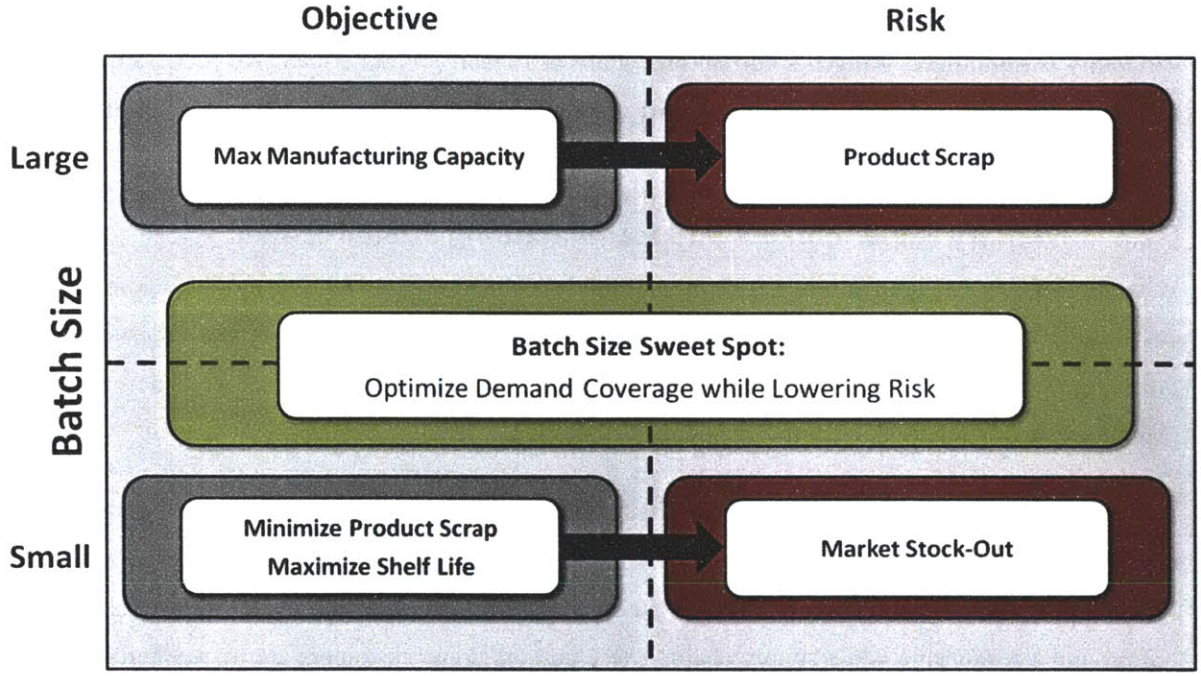


Figure 20 A "sweet spot" between high and low batch sizes accounts for demand and supply variability

Significant research around Economic Lot Scheduling Problem (ELSP) – or optimal scheduling of multi-product production while minimizing the sum of holding and setup costs – has been performed over the last 45 years. However, the optimal solution to this problem is complex and not accessible at a day-to-day manufacturing and supply chain level, as Amgen requires, for example. Furthermore, these solutions often times assume that products can only be produced within one manufacturing cycle (i.e., one iteration of a production plan), and that production rates are variable. Production rates are not variable in biotech manufacturing, however; these rates are tightly controlled and regulated as product quality can vary significantly with varied manufacturing processes, such as production rates.

More recently, Soman, et. al investigated ELSP with constant production rates and shelf-life considerations, which is believed to have applications to the food processing and – by extension, biopharma – industries. However, they too conclude that a solution that incorporates ELSP with shelf-life

constraints and sequence-dependent setups requires future continued research before it can be applied to industries (Soman, Van Donk and Gaalman).

While an optimal solution may not yet exist, Amgen has an opportunity to optimize its batch sizes by consolidating its various regional requirements to gain economies of scale in manufacturing, and to achieve lower costs per unit, so long as the risk of scrap or stock-out relative to demand and supply variability is minimized. Amgen's current procedure is a labor- and time-intensive process that relies on highly capable planners to analyze various demand, inventory levels and other product-specific characteristics, such as remaining shelf life.

5.2.3 Inventory Supermarkets and Manufacturing Postponement

While optimizing batch sizes may efficiently schedule lots and minimizing the sum of holding and setup costs, this approach is still vulnerable to variations in demand. With its international expansion, Amgen faces significant volatility in its high-mix low-volume markets, and so must consider an alternate planning system strategy that capitalizes on these variations.

As Lean production thinking and techniques have gained traction over the years, inventory has acquired a negative reputation that suggests masked operations problems and process shortcomings. However, as Reichhart et. al (and many other authors) argue, there is a balance between inventory used as a strategic buffer, and a responsive, agile supply chain. These authors argue customers are increasingly demanding supply chain responsiveness, which they define in the following way (Reichhart, Framinan and Holweg):

> *A system's responsiveness is the system's ability to "adjust its output within the available range of the four external flexibility types: product, mix, volume and delivery, in response to an external stimulus, e.g., a custom order" (Reichhart and Holweg).*

Furthermore, the authors defined the four external flexibility types – each of which applies to Amgen and its customers – in the following way (Reichhart, Framinan and Holweg):

> **Product Responsiveness**: ability to introduce new products or changes to existing products.
>
> **Mix Responsiveness:** ability to alter the product mix (within the existing product range) that the system delivers.
>
> **Volume Responsiveness:** ability to change the system's aggregated output.
>
> **Delivery Responsiveness:** ability to alter agreed delivery agreements (e.g., shortening lead times, changing the products' destination or its delivery sequence).

Reichhart, et. al surveyed and analyzed 37 automotive component suppliers to evaluate the concept of manufacturing responsiveness and its link to inventory, posing two survey questions to their subjects to measure responsiveness of their supply chain systems:

1. **To measure volume responsiveness:** "To what percentage could you increase your production level for the products that you supply to your main customer, within the specified time horizons (without compromising supply to other customers – estimates acceptable)?"
2. **To measure mix responsiveness:** "To what percentage could you alter your variant mix for your main products (e.g., blue headlamps with fog lights instead of red headlamps without fog lights) within the specified time horizons[18] (without increasing the unit costs substantially)?"

The results are plotted in Figure 21, which shows that a positive relationship exists between the level of finished goods (FG) inventory held at a certain point in the supply chain, and the level of the supply chain's upstream responsiveness (or the ability to execute short-term changes) (Reichhart, Framinan and Holweg).

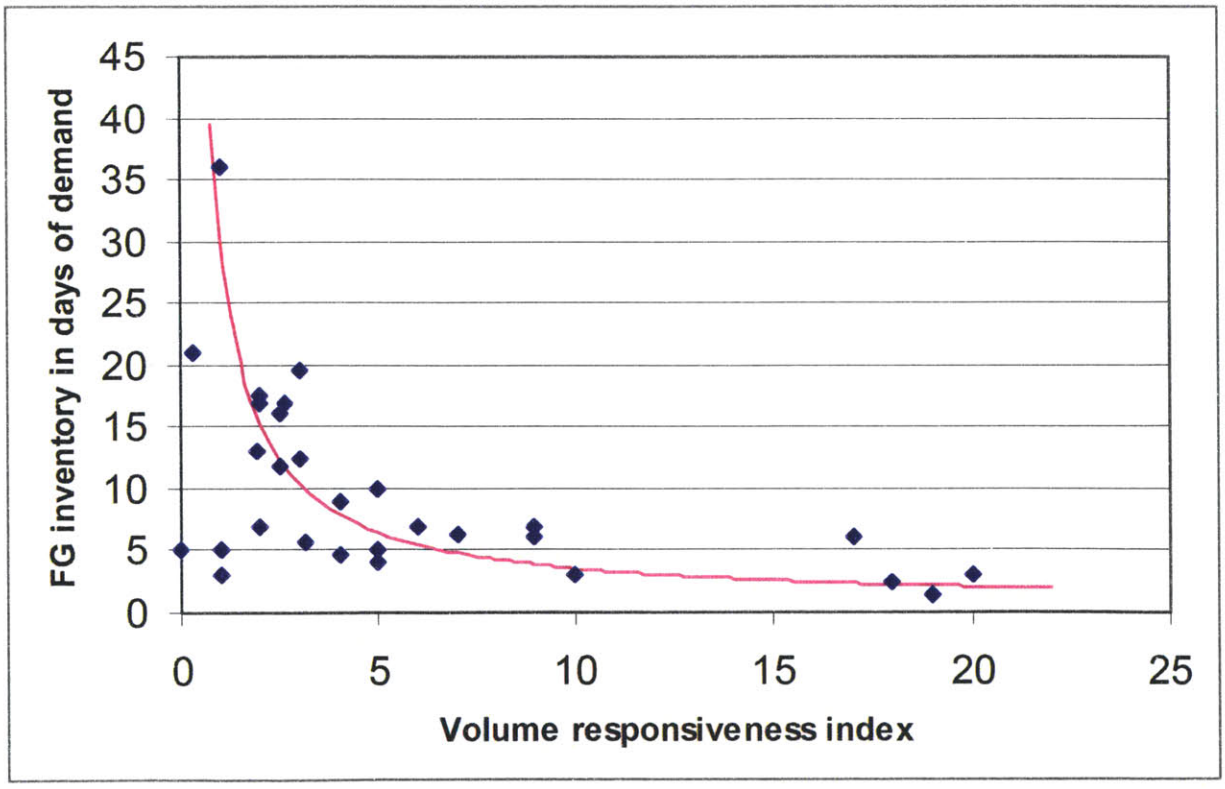


Figure 21 Relationship between finished goods (FG) inventory and volume responsiveness (Reichhart, Framinan and Holweg)

[18] The four time horizons were "same day (next shift)," "next day," "next week" and "next month."

Finished goods (FG) inventory must be considered differently in the face of demand variability, however; in this case, the FG inventory functions as a buffer between supply and demand, which is the essence of the inventory supermarket concept, shown in Figure 22.

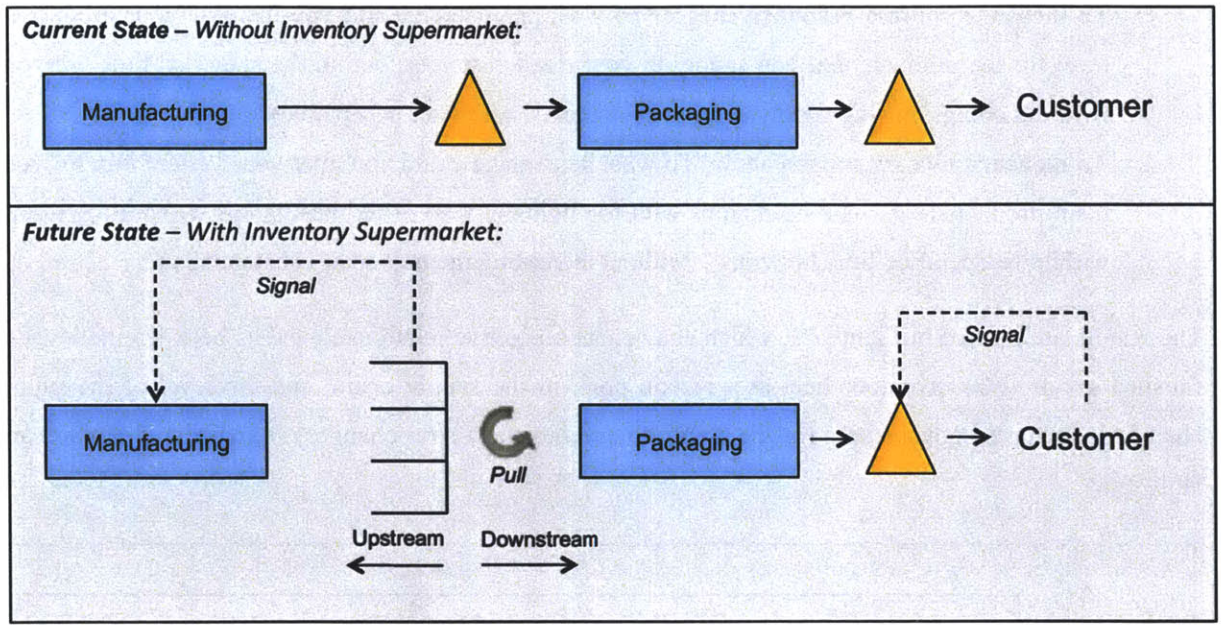


Figure 22 Inventory supermarket ("inventory buffer") conceptual representation relative to Amgen Operations

In Figure 22, a supply chain without an inventory supermarket (current state) is contrasted with a supply chain featuring an inventory supermarket (future state). In the top, or current state, representation, production is pushed via batch size production downstream through the process, where differentiated inventory sits at designated locations until a customer order is processed and inventory levels are depleted. This system is highly restrictive, however, in that it limits supply chain flexibility and agility. For instance, if a customer order varies and is larger than the amount of inventory in stock, production must begin at the initial upstream step, which creates a long lead time from the customer perspective.

In contrast, if a customer order varies and is smaller than what was forecast, a large amount of differentiated inventory will remain at various points in the supply chain. Holding inventory is not only expensive, but is also risky in terms of significant forecast error for a portfolio of products (i.e., differentiating too much of one product, and not enough of another product), high scrap rates and high expiry rates. This supply chain is neither agile, nor capable of withstanding supply and demand disturbances for long periods of time (Naylor, Main and Berry).

On the other hand, the bottom, or future state, representation represents a highly flexible and responsive supply chain. As shown in the figure, an inventory supermarket – or a buffer of inventory – separates two parts of the supply chain: the upstream portion, which is oriented toward the supply chain planning analysis, and the downstream portion, which is oriented towards customer orders. This decoupling point – or the inventory supermarket – is a point in the supply chain where undifferentiated material is strategically held to buffer production from volatile customer demand, ultimately smoothing production.

Downstream from the inventory supermarket, customers can "pull" material from the buffer, which is then quickly differentiated per the customer's specifications. Upstream from the inventory buffer, the planning organization turns on production to maintain an appropriate level of undifferentiated inventory within the buffer to satisfy forecast, aggregated demand from a variety of customers. Ultimately, this planning system allows the supply chain to rapidly respond to a wide range of demand in terms of both volume and mix, and ultimately reduces the lead time experienced by the customer (specifically for large or not-typically-stocked SKUs).

Perhaps the most important consideration when establishing the inventory supermarket is the placement of the decoupling point. This location must be an optimal balance between supply chain responsiveness and product differentiation, and should be located as far downstream as is possible, as articulated by Pagh et. al (Pagh and Cooper):

> *The notion of [an inventory supermarket or] manufacturing postponement is to retain the product in a neutral and noncommitted status as long as possible in the manufacturing process. This means to postpone differentiation of form and identity to the latest possible point.*

One of the most famous and thus classic examples of this type of manufacturing postponement / use of an inventory supermarket is with color paint at the retailer / customer level. Retailers were able to capitalize on – and despite of – varied customer demand by stocking only neutrally colored paint until a customer "pulled" a specific color order, at which point the retailer added customized coloring to the neutral paint per the customer's order. Ultimately, the number of SKUs the retailer had to hold was drastically reduced, and customers enjoyed the benefit of a responsive, agile supply chain (Pagh and Cooper).

Similar benefits were realized by a soluble coffee manufacturer that improved its supply chain performance by delaying labeling and packaging until customer orders were received, as detailed in the work of Wong, et. al. The company demonstrated it could reduce its aggregate inventory by up to 40% by employing various manufacturing postponement improvements, such as identifying all generic products and all products ultimately produced directly from the generic products.

To reduce inventory, the coffee manufacturer employed the Square-Root Law, formulated by Maister (1976), which quantifies the benefits of risk pooling and manufacturing postponement. That is, given N individual SKUs that have independent demand and that are identically distributed, upon aggregating demand, a manufacturer can expect a benefit of a $\sqrt{N}$ reduction in safety stock. In the case of the coffee manufacturer, significant reductions in inventory levels were realized simply by aggregating demand upstream and postponing differentiation until a customer order was received (Wong, Potter and Naim).

Amgen has a thorough understanding of its SKUs' demand patterns, which suggest segmentation. With this data, the company is equipped to take the next step that matches appropriate replenishment strategies, such as the inventory supermarket and decoupling points as suggested by Ebel, et. al, to each segment. As described in the next section, the internship focused on selecting an appropriate product to demonstrate the power – in terms of flexibility and agility – of inventory supermarkets.

6 Current State Analysis

While the US is still the main revenue driver for Amgen, as shown in Figure 23, international sales have increased from 17% to 23% over just five years (Amgen, Inc.); international sales will continue increasing with time.

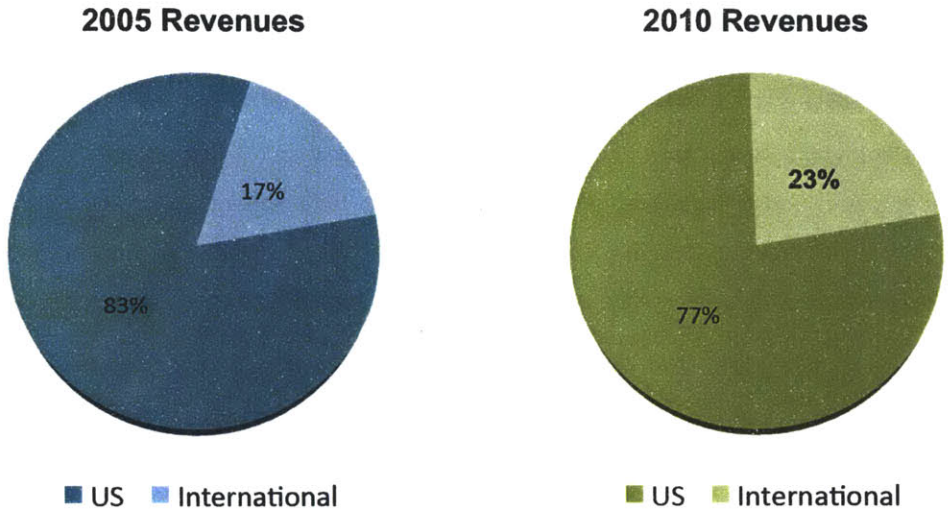


Figure 23 While the vast majority of Amgen's revenue is still collected from the United States, over the last five years, revenue from international customers has increased from 17% to 23%

This aggressive push to expand outside the US is rapidly influencing Amgen Operations: supply chain and manufacturing requirements are becoming increasingly more complex with each new market Amgen enters. Thomas Ebel, et al. well articulated these new challenges faced by the industry in a McKinsey article called *The Value of Flexibility: Pharma Supply Chain 2020* (Ebel, Großpietsch and Schrader):

> *Pharmaceutical companies have traditionally focused on quality and security of supply at the expense of speed and flexibility, where they trail other industries by a wide margin. As the market becomes more volatile and pressure on working capital increases, pharma companies need to rethink their approach to flexibility.*

Much of Amgen's international expansion is in high-mix low-volume (HMLV) markets. These markets often have unique packaging requirements – in terms of pack size and language, for example – which results in new SKU creation and thus added complexity to the supply chain. Furthermore, these new markets also frequently have both low-volume and volatile demand, which exposes Amgen's supply chain to a large degree of uncertainty in terms of forecasting and manufacturing planning. In one new market entry case, Amgen supplied a country with six months of projected inventory, only to find its

products sold out immediately within the first month; the company had to scramble to satisfy the new market's unanticipated demand requirements as quickly as possible, disrupting the supply chain and manufacturing plans in work at the time.

Amgen must develop a more flexible and agile supply chain to satisfy its international customers who require demand responsiveness and customized products. The internship aimed to develop a strategy that mitigated these two major challenges, which are described in more detail in the following sections.

6.1 Current Lead Time Limits Demand Responsiveness

In 2007, Amgen deployed a customized Lean initiative across its network in response to its rapid growth from both a company and Operations perspective. Madhu Balachandran, Sr. Vice President of Manufacturing, explained that the need for Lean thinking was rooted in the need for higher efficiency and demand responsiveness as Amgen increased its global footprint (Next Generation Pharma):

> *Our manufacturing plans had to be adjusted. We had to change our way of thinking. It was important for us to keep quality high, but...we had to gain additional efficiencies, and we had to get faster in the way we made and supplied products to our patients.*

Five years after introducing Lean across the organization, Amgen must now explore an additional paradigm: the concept of agility to improve demand responsiveness, especially to its newer, more unpredictable markets. The authors of *Leagility: Integrating the lean and agile manufacturing paradigms in the total supply chain* described Lean thinking and agile manufacturing, and why the distinct difference between the two makes both a necessary component of operational excellence (Naylor, Main and Berry):

- **Leanness** means developing a value stream to eliminate all waste, including time, and to ensure a *level* schedule.
- **Agility** means using market knowledge and a virtual corporation to exploit profitable opportunities in a *volatile* market place.

In the spirit of Leanness, a value stream map of one of Amgen's product's – referred to as "Product A" going forward – planning, manufacturing and distribution process was created with a team from a manufacturing site to understand the current state.

While the monthly planning cycle is a well-defined and well-executed S&OP-style process that occurs in parallel with all manufacturing planning and production, an opportunity for improvement exists within

the manufacturing planning, and manufacturing and disposition[19] phases. Without any exceptions (e.g., expediting lots to satisfy last-minute demand changes), the manufacturing planning process consumes 1.4 months, and the manufacturing and disposition process takes 1.5 months.

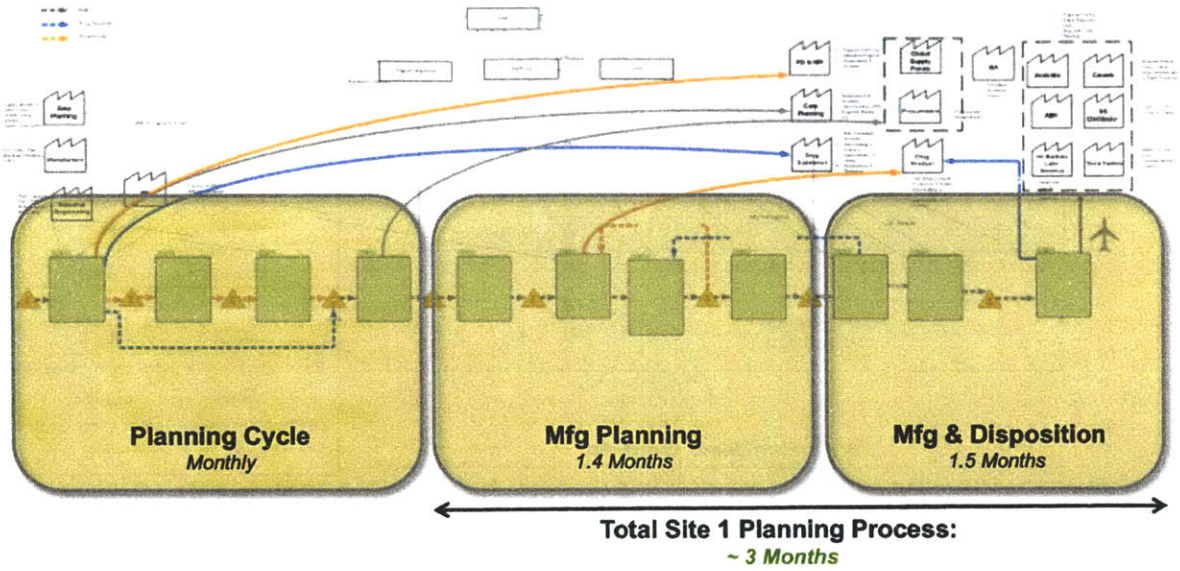


Figure 24 A value stream map of Product A's planning, manufacturing and disposition processes; note that the planning cycle phase occurs continuously and in parallel with the manufacturing and disposition processes

Ultimately, after placing an order, the expected lead time observed by a North American customer – the process from placing an order, then executing manufacturing from the DS stage to the FDP stage – is approximately three months. For international customers, the total lead time (from order placed to released for delivery) is much longer and can extend to nearly seven months, as shown in Figure 25.

[19] "Disposition" refers to the process that Amgen's Quality organization executes to review, approve and release manufactured product for distribution to customers.

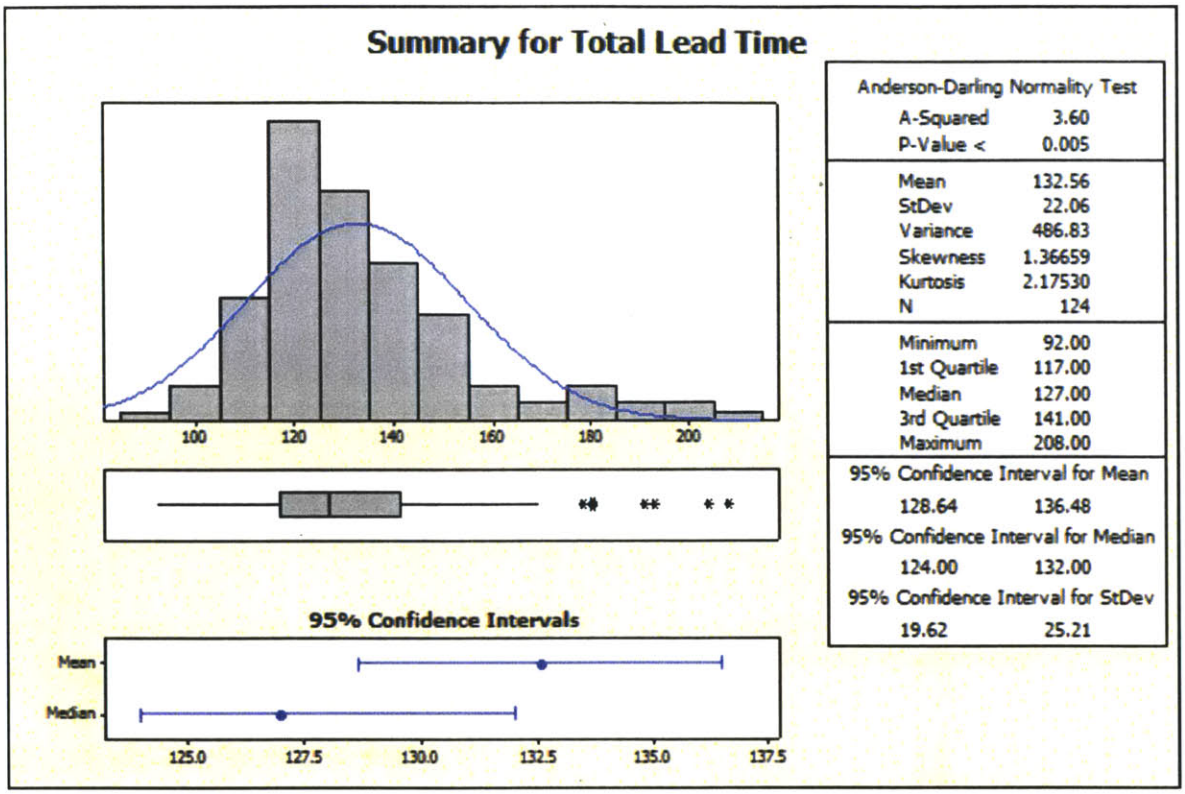


Figure 25 Observed lead times (from customer order to delivery date, or from customer order through manufacturing of DS to FDP) experienced by international customers

Extended international lead times – such as those lasting approximately seven months – are often times not due to the manufacturing process, but rather to uncontrollable events, such as noncomforances (NCs). Amgen's Industrial Engineers use control charts called Individual Value – Moving Range ("I-MR") to monitor this type of data. And I-MR displays individual observations in the top chart (e.g., total lead time for a lot) and the bottom chart displays the moving range, or the absolute difference between two consecutive observations. The combinations of both charts indicate whether a process is in control, or centered around the mean (green line) and within the control limits (red lines).

As shown in the I-MR in Figure 26, within the January 2011 to September 2011 timeframe, five individual lots exceeded the lead time upper control limit (UCL) due to nonconformances, which can typically consume anywhere from 10-90 calendar days depending on the issue, ultimately skewing the average lead time for products not affected by nonconformances. These NCs caused the process to become out of control, whereas the remainder of the process is relatively in control.

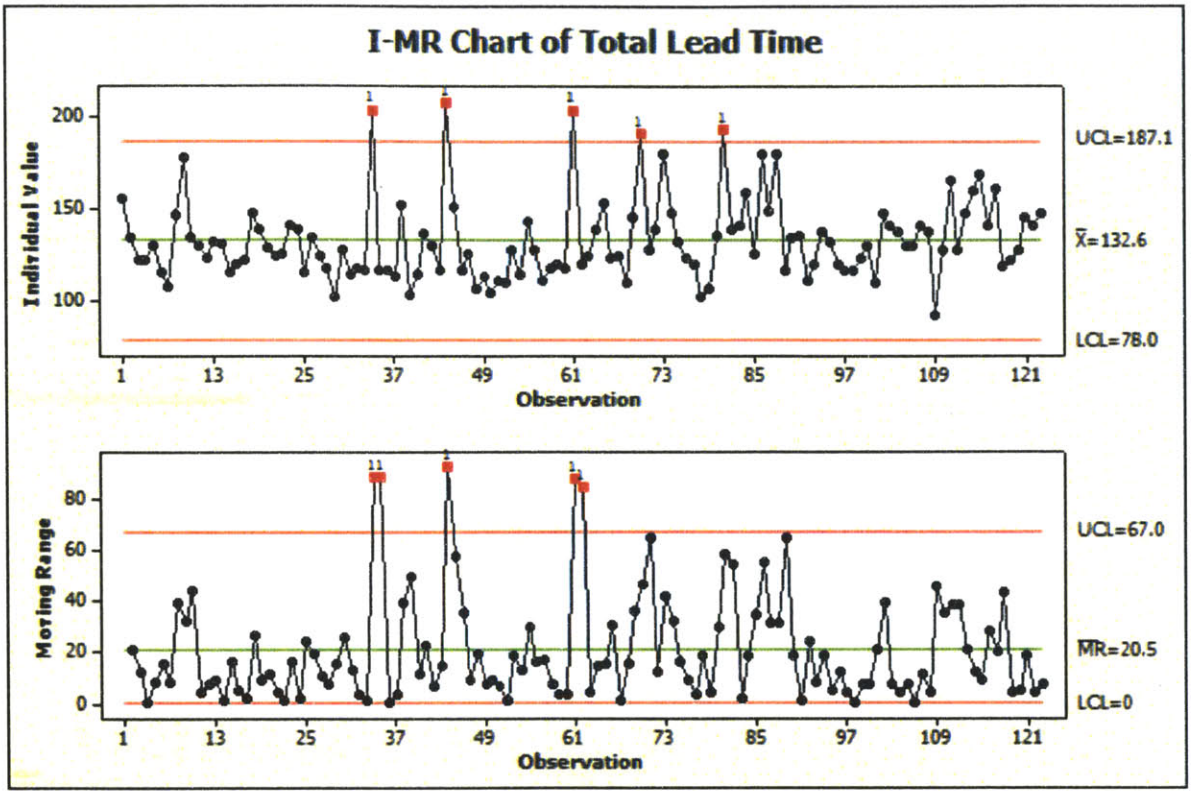


Figure 26 A control chart monitoring the observed international lead times (in calendar days) between order placement to product release, or when product can be shipped to the international customer

Furthermore, as shown in the boxplot in Figure 27, of the three processes – planning, manufacturing and release, and shipping – the manufacturing and release process has the longest lead time and the highest variability. Amgen can realize the greatest benefit by executing a reliable, flexible and agile improvement project at the manufacturing and release process stage.

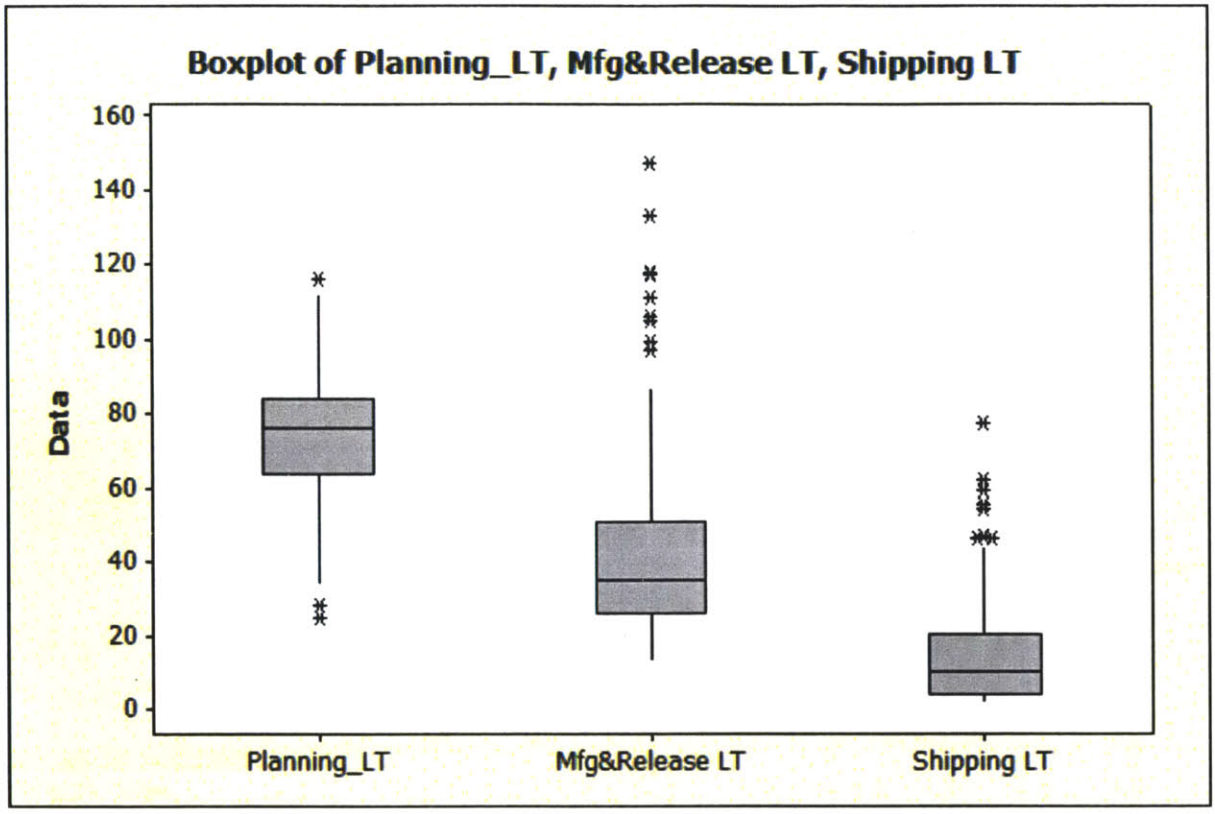


Figure 27 Boxplot of the planning, manufacturing and release, and shipping process lead times; overall, the manufacturing and release process has the longest lead time and the highest variability

Lastly, long lead times affect on-time delivery metrics, as committed deliveries are missed due to nonconformances or other manufacturing issues. Often times, if a lot is in jeopardy of being late for a delivery due to a nonconformance (which has an unpredictable release lead time), for instance, another lot is rushed through the supply chain and manufacturing in order to deliver product to the customer. Not only do missed deliveries affect Amgen's approximately 77.5% on-time delivery metric, as shown in Figure 28, but emergency rush orders disrupt the supply chain and manufacturing organizations, ultimately introducing inefficiencies and waste.

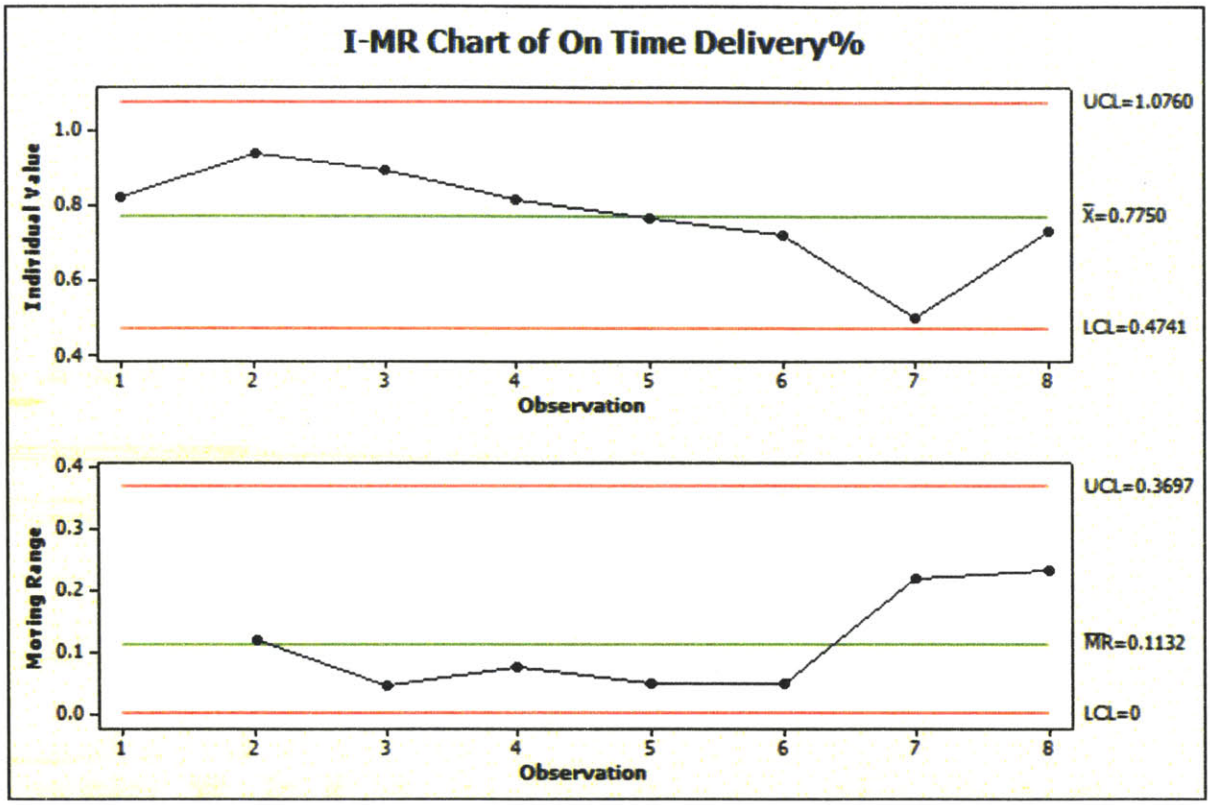


Figure 28 Control chart monitoring observed on-time delivery performance from January 2011 to September 2011

Whether three months or seven months, this lengthy cycle time limits demand responsiveness, and is especially restrictive for Amgen's growing emerging market customers, whose demand is often very volatile. To not only withstand – but also capitalize on – the variations and disruptions caused by volatile demand, Amgen must focus on the manufacturing and release process to shorten its lead time and lead time variability.

6.2 Low-Volume Lot Sizes Increase Changeover Impact and Scrap Risk

The concept of changeover impact described in section 5.1.4: Changeover Impact and Manufacturing System Design is especially relevant to Amgen's international expansion efforts. The new markets the company is entering into are often markets with low-volume, highly volatile demand and unique SKUs that increase supply chain complexity. This presents Amgen with an interesting challenge. On one hand, producing the largest possible lot (which might be anywhere from two to 1,000 times the market's actual annual demand) improves efficiency in terms of machine utilization, economies of scale and changeover minimization. On the other hand, however, producing large lots for markets with low-volume demand presents a significant and expensive risk related to expiry and scrap. Amgen must understand its entire

demand profile and investigate how it might be optimized to serve all customers while balancing efficiency with risk.

6.3 Constraints

Process improvements in the biotechnology industry are tightly constrained by both internal and external sources and affect manufacturing, distribution, market, product and cost specific details. The following is a list of constraints that were non-negotiable throughout the internship, and, as a result, required significant consideration to determine how best to optimize Amgen's supply chain despite the limitations.

6.3.1 Manufacturing Capacity and Flexibility

Amgen has a finite amount of manufacturing capacity, and the option to increase capacity is not a short-term solution. Adding additional manufacturing lines are on the order of millions of dollars in equipment costs, and significantly more in terms of regulatory certification time and expenses. Building an additional manufacturing facility is on the order of hundreds of millions of dollars and several years of lead time.

Specific products are certified by the regulatory agencies to be manufactured on specific lines; if products are not certified on a line, product cannot be manufactured on it. That is, if there are two identical manufacturing lines, but a product is only certified on one line, the product cannot be manufactured on both lines. This represents a significant constraint in terms of scheduling manufacturing runs, especially short-term scheduling changes in response to a spike in demand, for example.

6.3.2 Low-Volume Demand and Changeovers

As described in section 5.1.4: Changeover Impact and Manufacturing System Design, changeovers represent a significant portion of Amgen's available manufacturing time. As such, satisfying low-volume demand with dedicated lots is not a possibility, as this increases the changeover impact. The presence of low-volume demand represents a significant changeover / operational efficiency challenge for manufacturing.

6.3.3 Service Level

Like all firms in the industry, Amgen maintains an extremely high service level, which ultimately translates into significant safety stock levels and high inventory holding costs. The company does this not only to "serve every patient every time," but also to protect its market share, as alternative drugs exist in the marketplace. Market loss due to unavailable therapeutics is not a risk Amgen wishes to take. The service level is significantly high on the order of 99.x% to ensure virtually no possibility of stock out.

Maintaining this significantly high service level while minimizing scrap represents a challenge for both the manufacturing and supply chain functions.

6.3.4 Remaining Shelf Life

In general, Amgen's products all have an allowable remaining shelf life (RSL) before the material expires and is thusly unusable for human consumption. On top of this, however, various countries' contracts call for longer RSLs[20] upon product delivery. Typically, Amgen delivers products with approximately six to nine months RSL to markets with high-volume and stable demand. For emerging markets, for instance, Amgen might contract RSL of 12 -18 months.

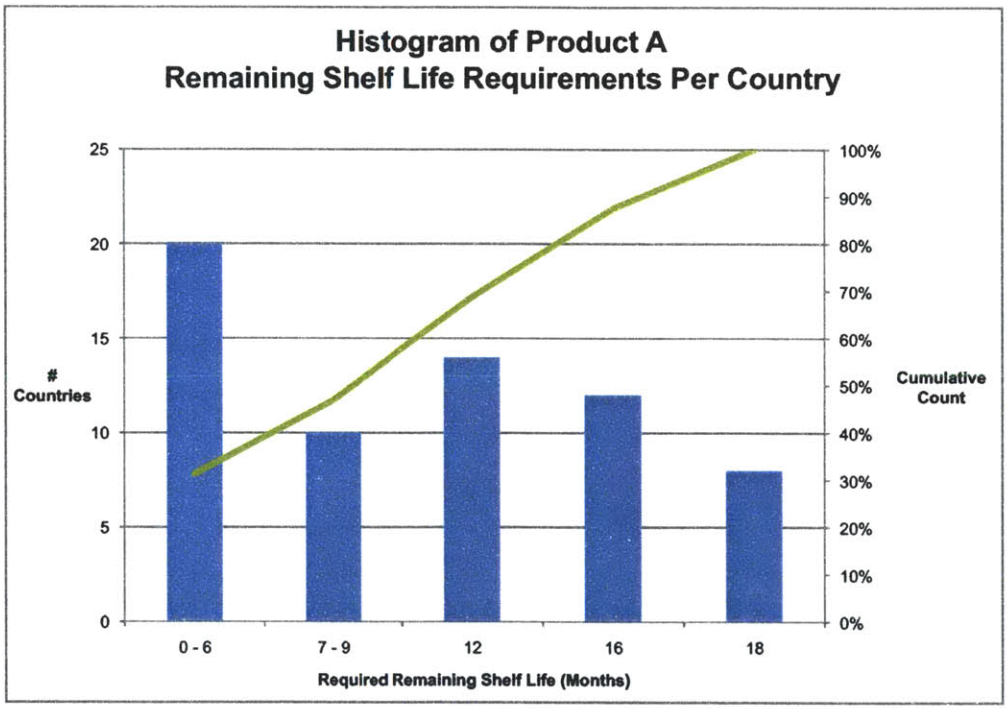


Figure 29 Countries require specific remaining shelf lives, which can range from six months to 18 months

As shown in Figure 29, Amgen manages a range of RSL requirements for Product A, where, from an Amgen perspective, only 30% of countries require a very manageable six month RSL, yet another 30% of its customers require more limiting 12-18 month RSL. The wide range of RSL requirements create an additional level of complexity that Amgen has to manage within each product line. Furthermore, the longer RSL requirements present a challenge considering the product has, in general, a 24-month lead

[20] This is typically seen in contracts with emerging markets, as demand for the drug is either uncertain or highly erratic. These countries required a long remaining shelf life in order to buffer against this variability.

time after completing Fill (i.e., filling a vial of PFS with the drug substance), and the remaining manufacturing and distribution lead time after this can be significant.

6.3.5 Safety Stock

Amgen uses safety stock in various forms (DS, IDP, FDP) to buffer against variability in both supply and demand, and for strategic reasons, such as to buffer against natural disasters, contamination or other unpredictable events. As shown in Figure 30, Amgen splits its safety stock into two parts: Operational Safety Stock (OSS) and Strategic Safety Stock (SSS).

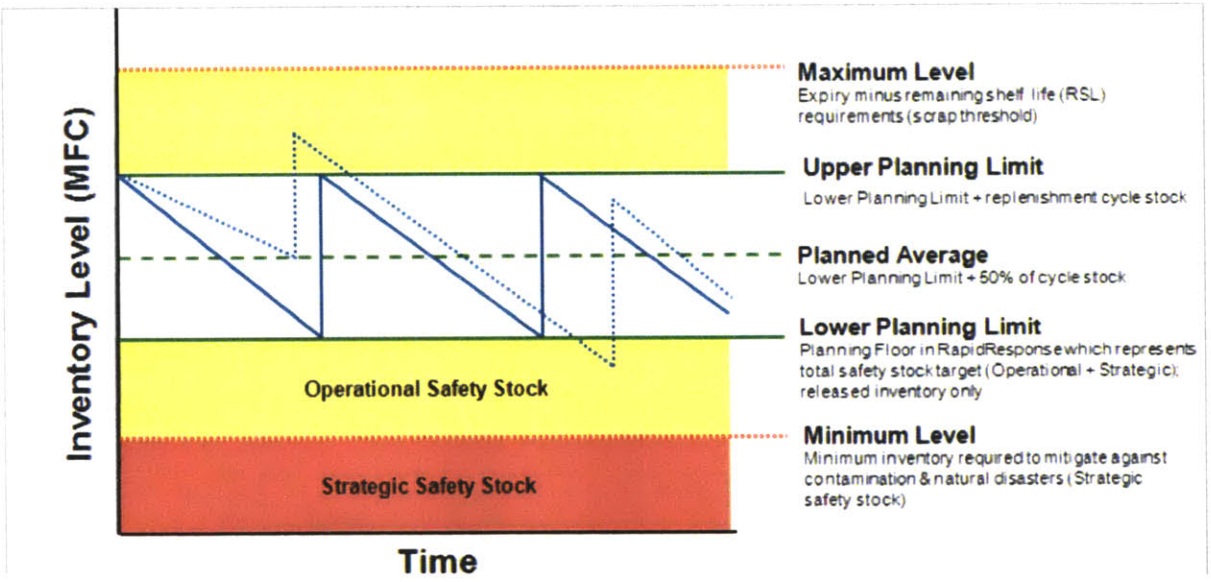


Figure 30 Conceptual representation of Amgen's inventory levels, including planning and safety stock limits (Amgen, Inc.)

Operational Safety Stock is used to buffer against supply and demand variability, and represents an inventory floor in Amgen's planning systems and procedures. Strategic Safety Stock is used to buffer against one time, unplanned events, and is generally not available for use under any circumstance other than an emergency. Because both safety stocks must remain fresh, Amgen must not only maintain the levels of safety stock, but it must also manage the material freshness, constantly rotating inventory in and out of safety stock.

6.3.6 Long Lead Times

As discussed in section 6.1: Current Lead Time Limits Demand Responsiveness, Amgen has significant end-to-end manufacturing lead time. Optimizing long lead times with respect to other constraints like remaining shelf life and safety stock levels represents a significant constraint.

6.3.7 Scrap

As in almost any manufacturing environment, Amgen closely monitors and strives to minimize scrapped material. The company invests a significant amount of time, labor and therefore costs into producing its expensive therapeutics, presenting a significant challenge to supply chain in terms of forecast accuracy.

6.4 Inventory Supermarket Adoption

Upon realizing that the internship project was similarly being investigated on a more practical level at a manufacturing site, the corporate-based team partnered with the cross-functional site-level team to pursue an enhanced "network" perspective and solution. Before partnering, however, the site-level team had analyzed their high-mix low-volume manufacturing challenges and decided that an inventory supermarket was the best solution to mitigate these challenges. As such, the newly formed "network team" adopted the inventory supermarket concept and moved forward to understand the data, equations, people and processes required to make this concept a reality.

Significant data shows that the main opportunity for improvement lies within the manufacturing and release process stage, specifically from the IDP stage to product release. As such, the team concluded that the inventory supermarket decoupling point would be most effective if placed after the IDP stage, before product moves to the labeled / packaged drug product stages (LDP / FDP). The team moved forward with the following inventory supermarket goals, as guided by Naylor, et. al in their article *Leagility: Integrating the lean and agile manufacturing paradigms in the total supply chain* (Naylor, Main and Berry):

- Supply chain / manufacturing processes upstream from the decoupling point should adopt Lean manufacturing paradigm and focus on level scheduling.
- Supply chain / manufacturing processes downstream from the decoupling point should adopt the agile manufacturing paradigm and focus on satisfying high-mix and highly volatile demand within a short lead-time.

7 Pilot Project Product Selection

In the article *Supply Chain Yoga*, Marco Ziegler, et al. of McKinsey & Company (Ziegler, Schrader and Ebel) described a common problem across the pharmaceutical and biotechnology industries that Amgen finds itself challenged by, as well:

> *Today, market growth is driven by line extensions and niche drugs that result in greater supply chain complexity. In addition, global growth is shifting to emerging markets, where distribution channels are more opaque and demand is highly volatile.*

As Amgen expands internationally, broadens its manufacturing and distribution network, and enhances its drug substance specifications, its supply chain is becoming more complex. The internship focused on developing a strategy to mitigate the challenges of an unresponsive supply chain and the risk of scrapping material in the face of growth.

To explore possible solutions and the feasibility of a strategy, a pilot project focused on a single product was targeted. The following sections describe three main considerations that were addressed to select an appropriate product for the pilot project to ensure a feasible and scalable solution was developed. Product A was ultimately selected from a small pool of products under consideration using the following criteria: product complexity, demand profile and variation profile.

7.1 Scope Description: Fill / Finish

This thesis targets the Fill / Finish manufacturing process, which is described in detail in section 2.3.2: Fill / Finish Manufacturing Stages. The scope of the internship impact was limited to these process steps for several reasons. First, a portion of manufacturing was selected to focus the internship; the end-to-end manufacturing process is too extensive to effectively analyze during a six-month internship. Second, it is during these downstream manufacturing steps that product complexity begins to significantly increase, a major and growing issue with international expansion. During previous steps, the product is manufactured in bulk and stored in large production vessels; it is not until Fill / Finish that product is differentiated per characteristics such as manufacturing location, drug concentration, language, pack size or testing requirements.

7.2 SKU Complexity

A product that represented Amgen's overall current state was desired for the internship so that it would represent the company's complexity challenges from a broad perspective. However, many of Amgen's products – in particular, its legacy products – have extremely high complexity in comparison to its newer

products with still growing distribution networks. To limit the level of complexity so that the project was understandable and manageable, the selection process was initially limited to newer products with smaller distribution networks.

To understand the level of complexity for various products under consideration, a "SKU tree" was created that detailed SKU proliferation throughout Fill / Finish manufacturing, or the process including drug product (DP), intermediate drug product (IDP), labeled drug product (LDP) and final drug product (FDP). Using demand data from Amgen's SAP cloud interface, RapidResponse, the relationships between SKUs up- and downstream were made. Some manufacturing bills of material cite certain upstream SKUs, while others do not; this is a function of regulatory filings and other governmental restrictions, and is reflected in the SKU tree design.

Several products were investigated at the SKU tree level to determine which product was least complex for the internship application. As shown in Figure 31, the number of SKUs for Product B increases at each process step[21]: DP has four SKUs, IDP manages 10 SKUs and FDP has 15 SKUs which are distributed to anywhere from one to 24 countries. Furthermore, SKUs are spread across multiple manufacturing sites (AFR, AML and ABR) or distribution networks (Market X). The SKU tree for Product B is incredibly complex with many interrelationships between SKUs, yet is only the tip of the iceberg in terms of the complexity that Amgen manages on a day-to-day basis.

[21] The LDP stage is typically not used; most products transition directly from IDP to LDP.

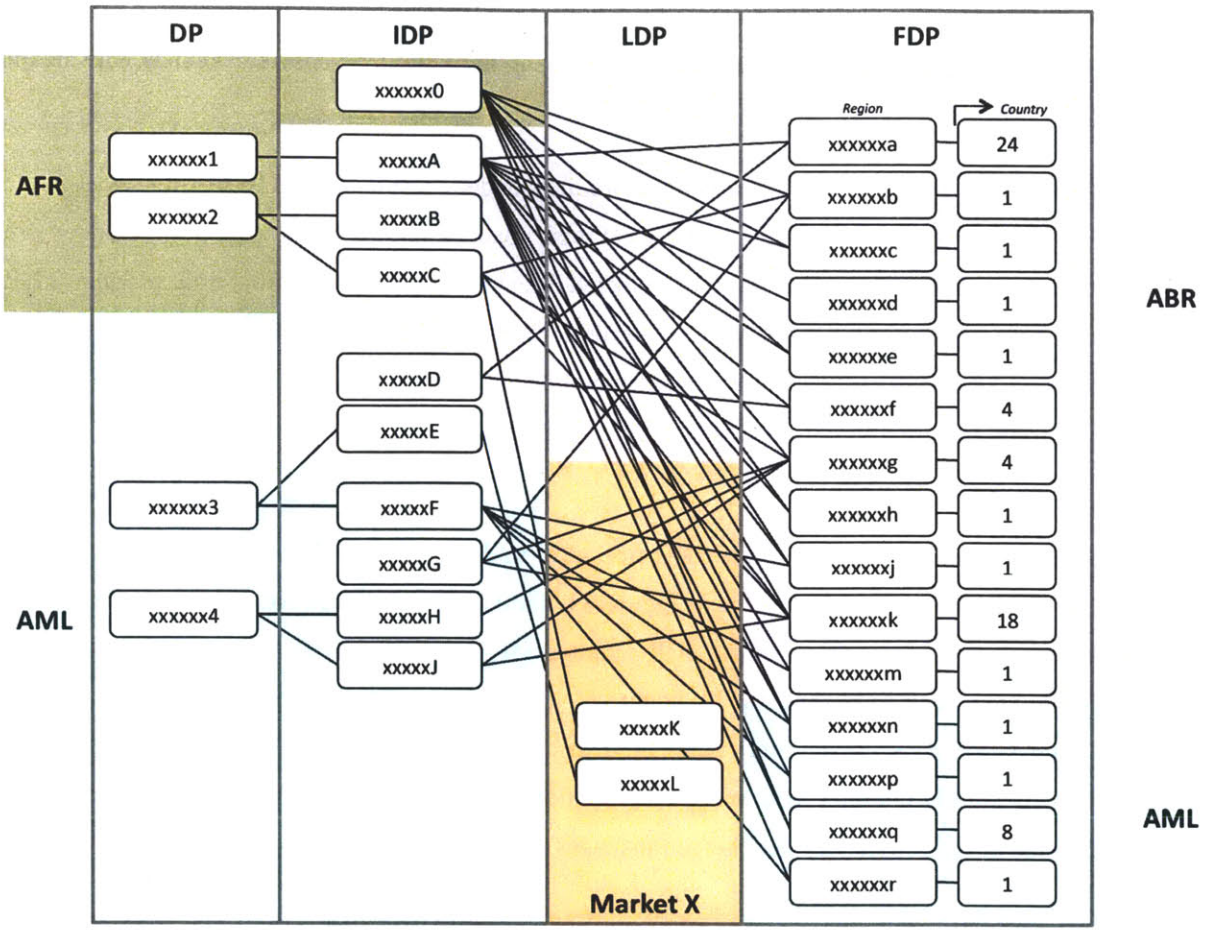


Figure 31 The SKU tree for Product B is of medium complexity; many of Amgen's older, more established products are many times more complex in terms of number of SKUs, SKU relationships and distribution networks

Creating SKU trees was an interesting and valuable exercise as it paints an end-to-end picture of the Fill / Finish manufacturing process that is otherwise relatively unknown at solely a site level. For instance, while a site (e.g., AML) might perceive SKU complexity as relatively low due to few SKUs at the drug product (DP) level, the complexity downstream quickly explodes and is managed by another site (e.g., Market X distributor or ABR).

Understanding the web of SKU relationships is critical. A small change at the DP level may appear to be deceptively low impact from a DP perspective (or from the AML site perspective), whereas the downstream effects at the FDP stage are exponentially magnified given the SKU complexity. Furthermore, keeping the relationships between SKUs straight (i.e., understanding exactly what upstream SKUs are and are not permitted for a particular country per testing requirements, the MBOM, etc) is a

risk-prone, energy-intensive process, requiring many resources like planners to ensure the product complies with jurisdictional requirements.

Ultimately, Product A was deemed to have the most manageable and appropriate SKU tree for the pilot project. As shown in Figure 32, Product A features a cluster of three interchangeable SKUs at the DP level, which splits into two clusters of interchangeable SKUs at the IDP level (to accommodate the North American market versus the rest of the world), and then becomes increasingly more complex at the FDP stage as SKUs proliferate by commercial organization (first FDP column), then distribution region (second FDP column) and then by country (third and forth FDP columns).

While there are over 50 FDP Product A SKUs, the SKU tree shows relatively linear SKU proliferation (i.e., there are no crossing lines, indicating relative downstream simplicity and straightforwardness), making the process of assessing the supply chain more manageable.

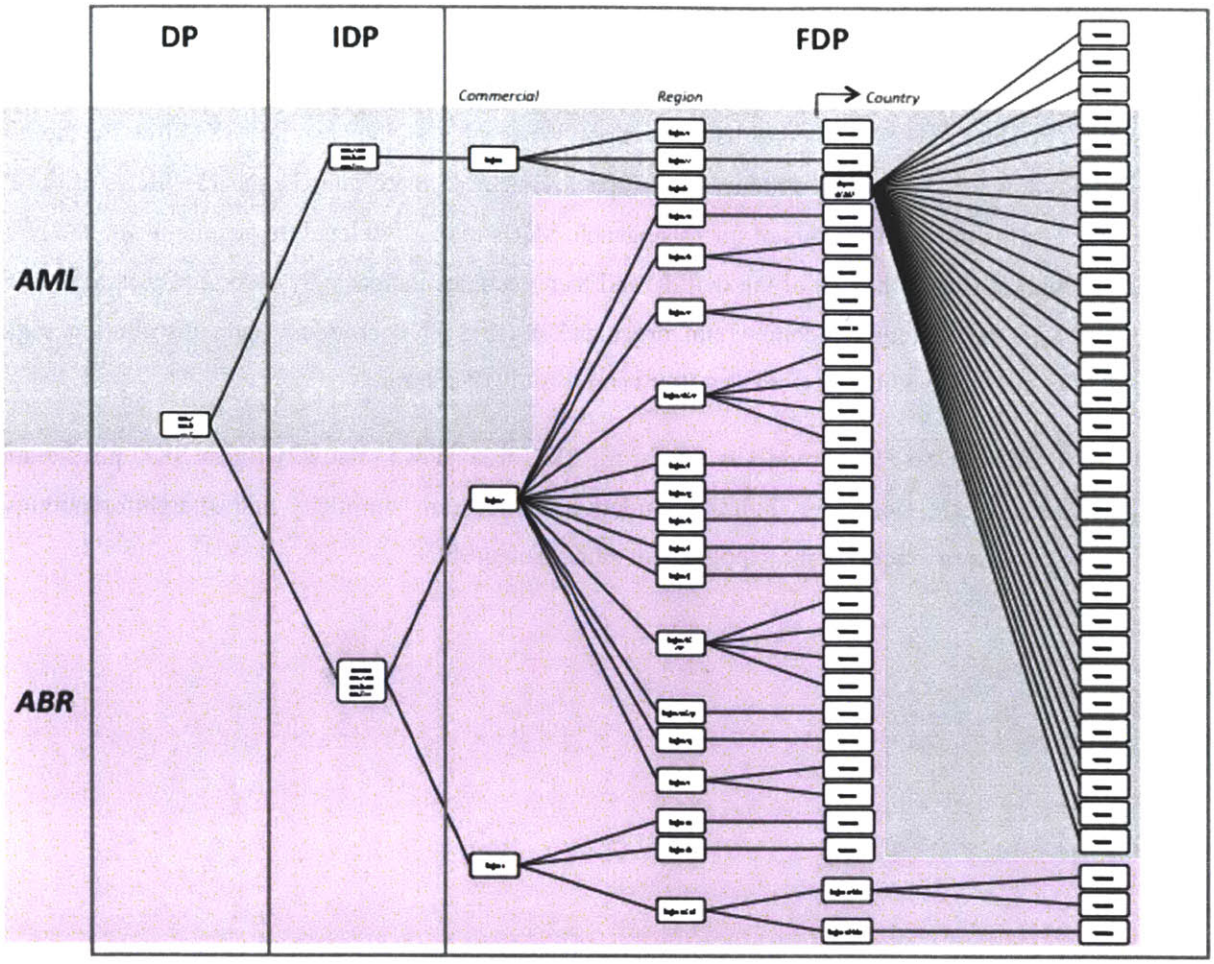


Figure 32 The SKU tree for Product A has relatively low complexity, and has linear and straightforward SKU proliferation

The most important feature of the Product A SKU tree to understand is that AML has not historically managed complexity, as it serves primarily the DP and IDP stages, not the FDP stages. However, AML's FDP SKUs – those shaded grey in the forth FDP column – are rapidly increasing in both number and volume as Product A enters additional markets that are to be served by AML. While ABR currently manages high complexity at the FDP stage (those SKUs shaded purple in the third and forth FDP columns) and has for quite some time, AML is not accustomed to this complexity. As such, the manufacturing site must prepare to manage downstream complexity both effectively and efficiently.

To evaluate whether an inventory strategy could be developed for Product A, the demand profile was evaluated. First, as previously mentioned, Product A is entering new markets at a rapid pace; as shown in Figure 33, it will be serving 68% more countries within a year's time[22]. The manufacturing site AML is

[22] Measured from December 2011.

primarily responsible for producing and distributing the majority of these added SKUs, introducing additional complexity to a manufacturing site that hasn't traditionally been responsible for such a large magnitude of SKUs.

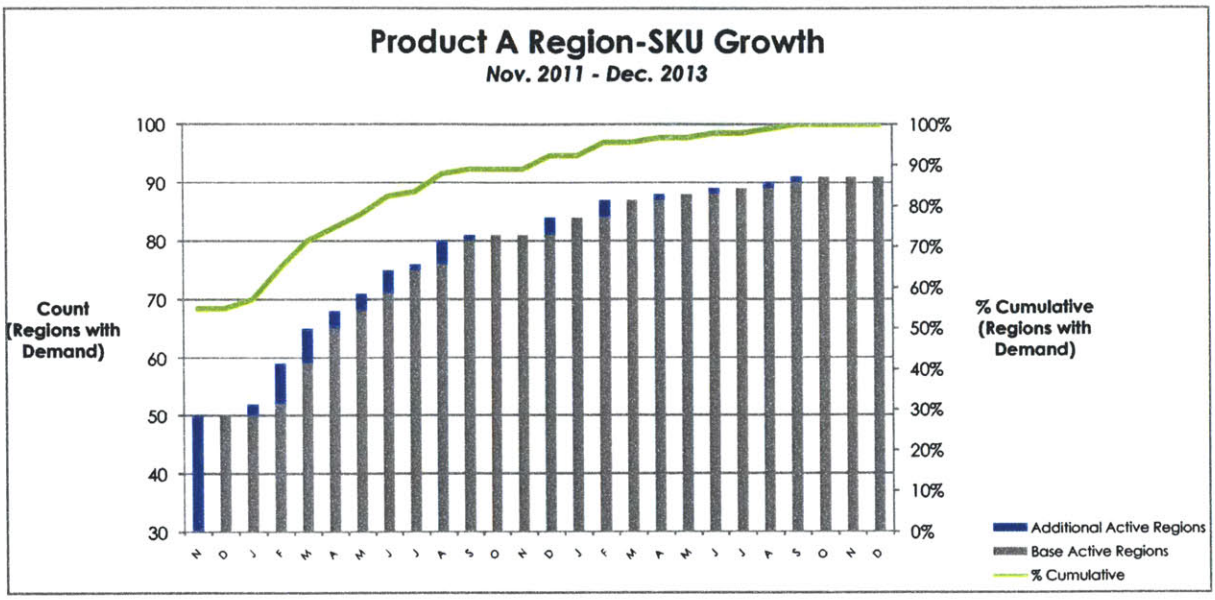


Figure 33 Product A will serve 68% more countries within one year from December 2011

It is therefore critical to develop a strategy that not only manages, but also capitalizes on, increased complexity. Otherwise, the manufacturing sites will be unable to satisfy increased demand and manufacture the required level of variety in an efficient manner.

While the number of countries served by Product A is increasing, the specifications of the product are also increasing. The leftmost box in Figure 34 shows a relatively simple "current state" at the time of the internship: two drug substance (DS) SKUs exist, which translate into two drug product (DP) SKUs. These DS SKUs are relatively interchangeable with only a few exceptions, so complexity is relatively low.

However, starting in Q1 2012, Amgen plans to enhance its current DS, resulting in a new SKU. This new SKU propagates downstream through the manufacturing process, adding another layer to the aforementioned SKU tree. Six months later in Q3 2012, Amgen plans to again enhance its DS, adding yet another layer of complexity to the SKU Tree. Finally, in Q3 2012, Amgen will execute one final enhancement to its DS, adding an additional third layer of complexity to the SKU Tree. Ultimately, the first three DS SKUs will be phased out. However, an already complex system will become increasingly more complex as upstream specifications rapidly change and affect all SKUs downstream.

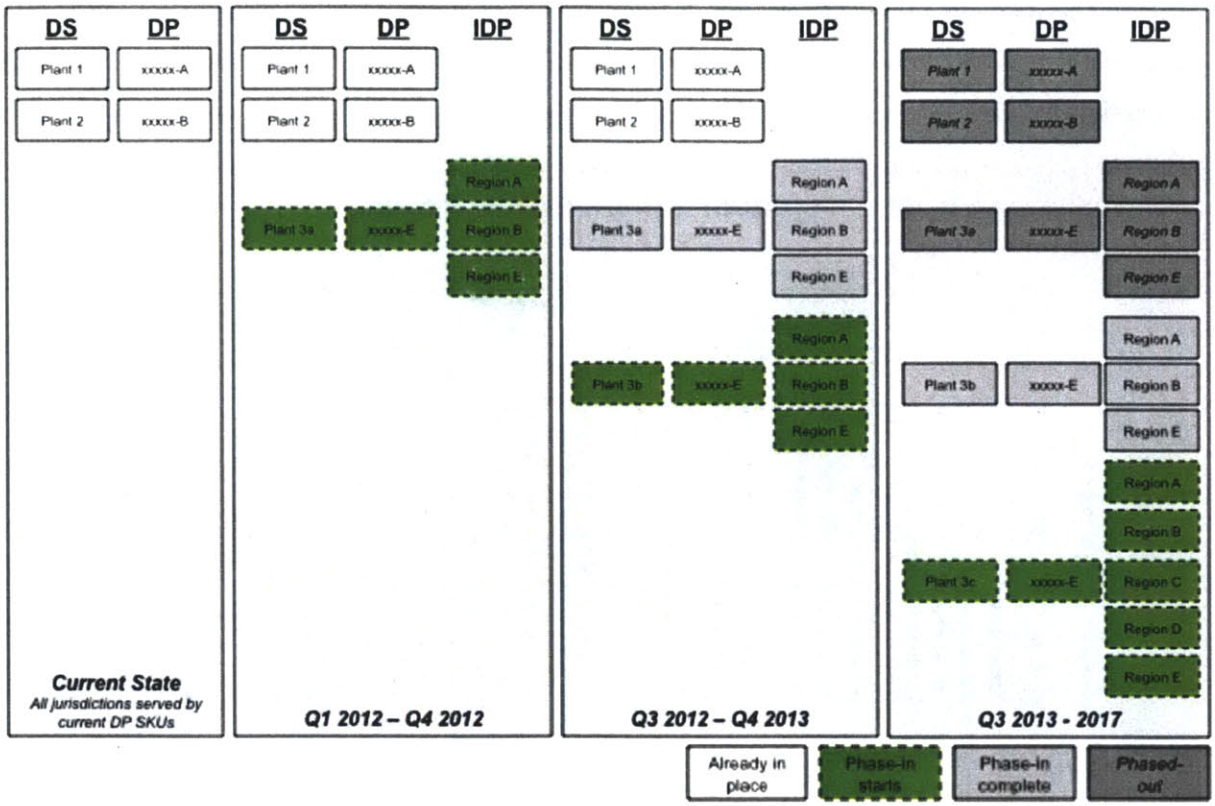


Figure 34 Product A's complexity will increase as DS specifications change through 2017

Whether Product A's complexity is increased by entering a new market, or by a change in the DS specifications, the product is rapidly become more complex. A strategy to manage this complexity is critical.

7.3 Demand Profile

To understand whether Product A was an appropriate selection for a high-mix low-volume (HMLV) strategy, the demand profile was evaluated. Figure 35 was created using demand forecast data for Product A.

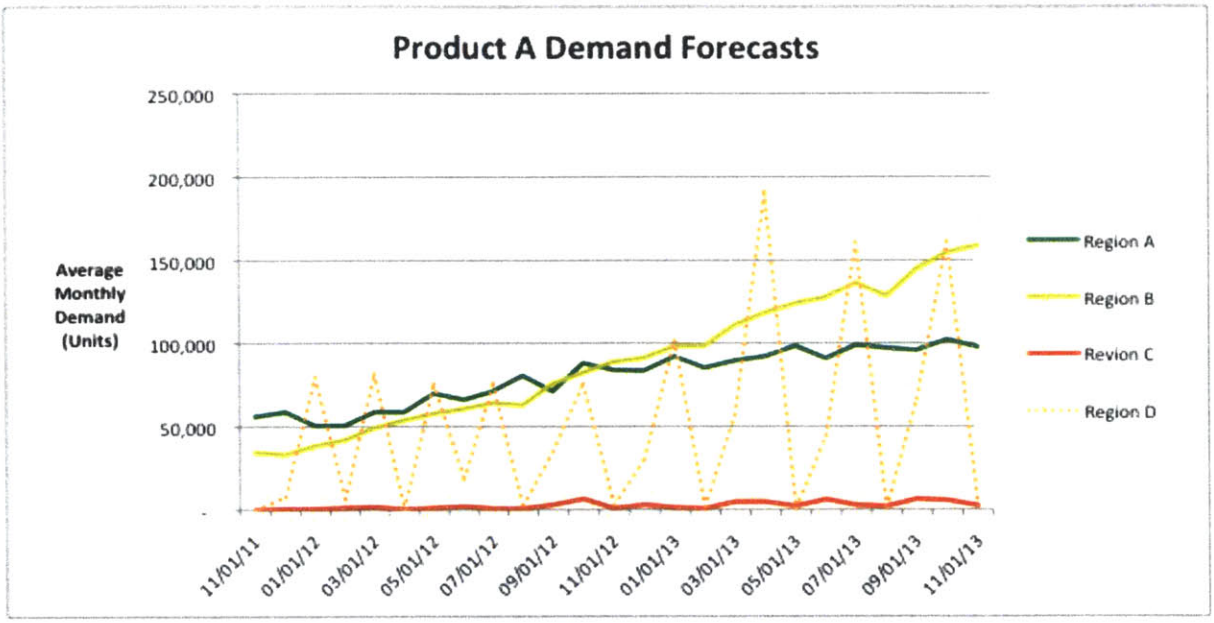


Figure 35 Product A features a variety of demand profiles within its portfolio: high-volume, stable demand (Region A and Region B), low-volume, relatively stable demand (Region C) and volatile, high-mix demand (Region D)

As shown in Figure 35, Product A has a variety of different demand segments: it features high-volume, stable demand (Region A and Region B), low-volume, relatively stable demand (Region C) and more volatile, high-mix demand (Region D).

This same type of segmentation can be seen in terms of variability, and there are various ways these segments might be accommodated by planning systems. The statistic Coefficient of Variation (CV) is useful for normalizing variability data to evaluate standard deviations for data with different mean values. The CV is computed using the following equation:

Equation 2 Coefficient of Variation (CV)

$$CV = \frac{\sigma_i}{\mu_i}$$

Coefficients of Variation can be thought of as a percentage of variability. For instance, for a product with annual demand of 35,000 units and annual standard deviation of 6500 units, the coefficient of variation is 0.186, or, in other words, the standard deviation is 18.6% of the mean. In this case, variability is considered low in comparison to other more volatile demand profiles.

As shown in Figure 36, a variety of demand profiles with respect to variability[23] exist, and there are different planning systems that apply to each of these segments. For instance, the high-volume, more stable demand is best suited for build-to-stock type planning systems. The lower-volume, yet still stable, demand is well suited for a pull type planning system. And lastly, the low-volume and higher variability demand might be served best by a make-to-order system.

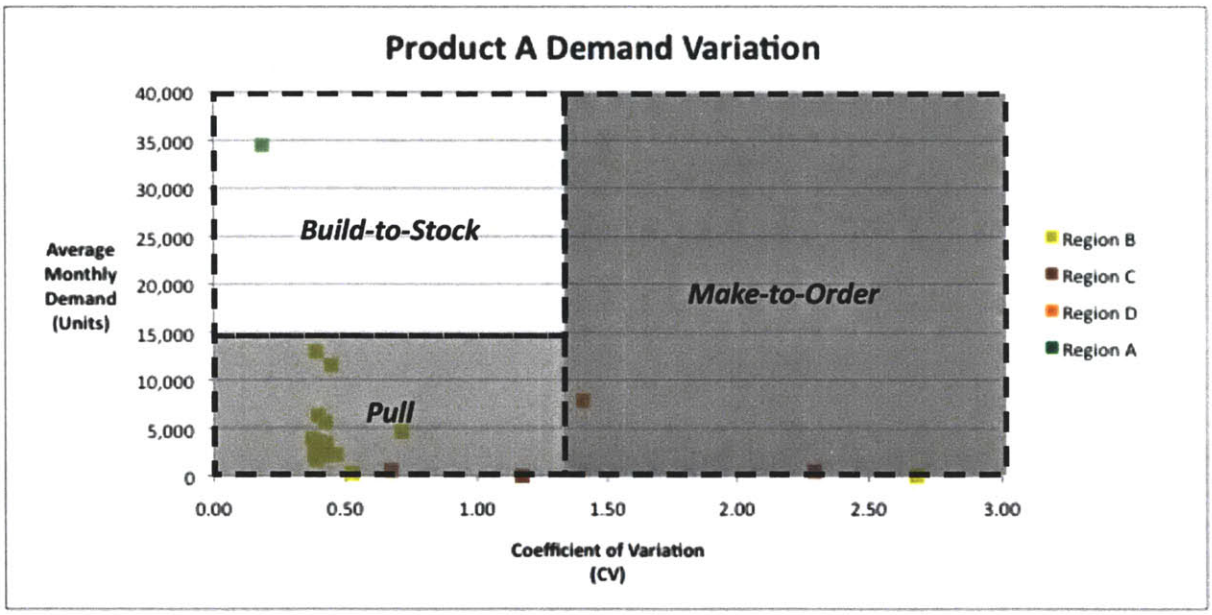


Figure 36 Product A also features a variety of demand profiles in terms of variation; each demand profile may be best served by a specific planning system

It was desired that the strategy developed accommodate all demand segments, rather than just the pull segment, for instance – this is a strategy that Product A can support.

7.4 Testing Requirements

Biotechnology is a strictly regulated industry. Everything from drug development to manufacturing procedures to product marketing is regulated by the United States Food and Drug Administration (FDA), and by similar agencies abroad. The testing and disposition processes for Amgen's production batches is no exception, and are subject to rigorous regulatory and testing requirements.

[23] Product A's coefficient of variations are calculated over a 24-month period.

Amgen produces products for many different jurisdictions, or markets (e.g., US, Europe, specific countries, etc), that may each have different testing specifications and requirements. To manage this complexity, Amgen tests on-site to a rigorous, internal specification that encompasses all jurisdictional requirements, and issues one certificate of analysis to certify the product is as intended. However, for some jurisdictions, once the product leaves Amgen's manufacturing facilities, more testing must be performed to validate the product. This is the case in Europe, for example, where the product must be tested on European soil before it is allowed into the region for distribution and sale. This additional testing requirement not only adds to the lead time, but also limits global flexibility. That is, product is typically designated for European distribution well upstream in the process, and cannot be used in other markets like the US or other small volume emerging markets.

To implement an inventory supermarket, it is imperative that material be as flexible as possible as far downstream as possible. As such two high-level options were identified to support Amgen's inventory strategy:

- **Duplicate Testing**: Test every lot per the internal Amgen specification and per all jurisdictional testing requirements.
- **Dedicated Testing**: As is the case today, test each lot per the internal Amgen specification and per its intended jurisdictional testing requirements, as required.

The duplicate testing option is an ideal case. This option allows all material to be certified identically regardless of the final customer, providing complete supply chain flexibility. This is an especially attractive option from an emerging market standpoint, because it allows Amgen to satisfy volatile, low-volume demand quickly and with the freshest[24] material possible, regardless of a pre-determined ultimate destination. The main weakness of this option, however, is that testing both per an internal Amgen specification and to a jurisdictional-specific specification (e.g., European specification) creates a potential for conflicting lab data, rending the material unusable. Furthermore, the option creates additional lead times, as an additional jurisdictional test is performed for every lot, and therefore leads to additional costs. While this may be an ideal option for Amgen in the future, especially if it can streamline its testing and consolidate to one testing location, this option is not feasible to implement near-term.

The other option, dedicated testing, is in place today. In this case, material is always tested per an internal Amgen specification before it leaves the plant site, and is only tested again if a jurisdiction requires this (as is the case for Europe, for instance). While this option doesn't provide complete supply chain flexibility, it balances cost with flexibility by enabling some globally released product (for those

[24] "The freshest material" refers to material with the longest remaining shelf life.

jurisdictions that don't require additional testing) and some dedicated-market product (for markets like Europe that require additional testing).

Maintaining a duplicate testing strategy with an inventory supermarket, however, requires the presence of not one, but two inventory supermarkets. As shown in the current state per Figure 37, today manufacturing produces material and then pushes it downstream through required testing procedures until the material eventually sits in inventory, either at the IDP stage or the FDP state. In the future state with duplicate testing and inventory supermarkets, however, completely tested inventory will remain in IDP inventory supermarkets until a customer pulls an order. The jurisdictional-specific inventory supermarket is refilled only when inventory dips below a certain level, turning on the manufacturing process.

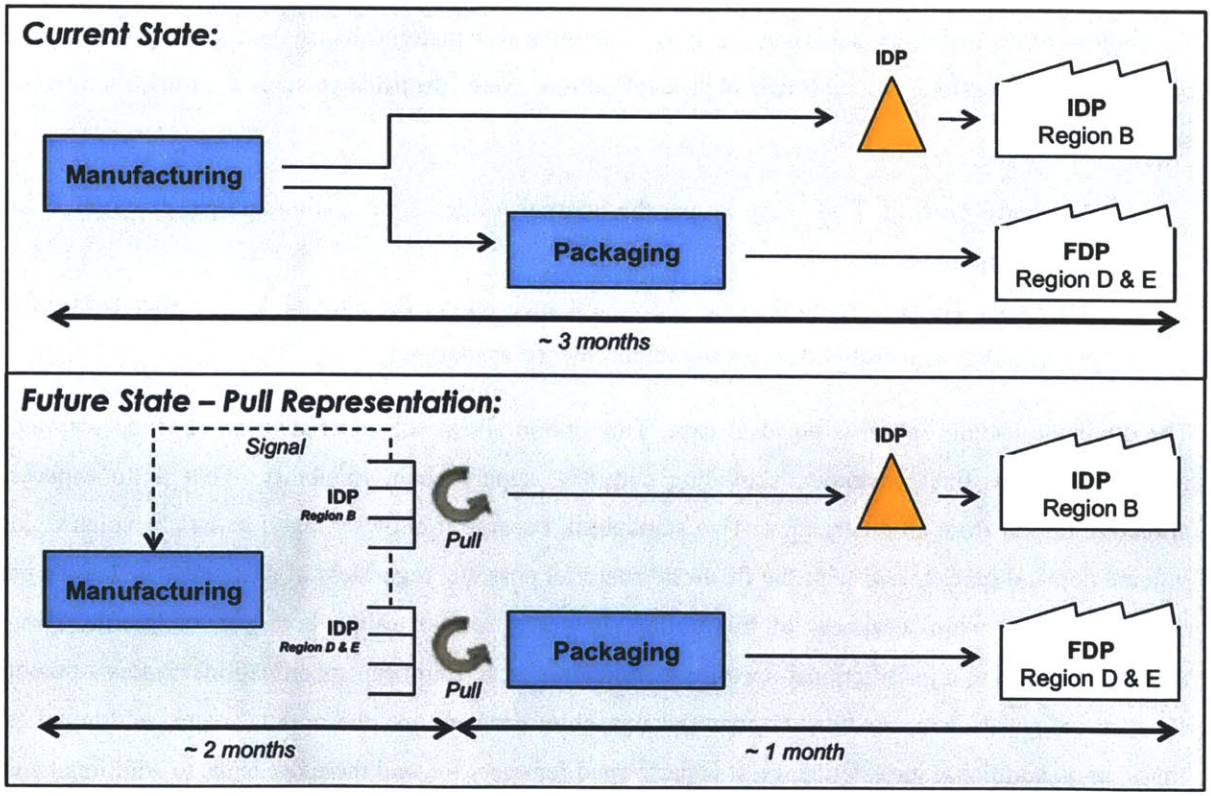


Figure 37 Amgen's current state versus a future state vision, tailored to accommodate a duplicate testing strategy

The main benefit of a dual-supermarket strategy is that it complies with jurisdictional testing requirements while still offering the benefits of an inventory supermarket. Specifically, per each jurisdiction, customers will realize shorter lead times (approximately one month, versus the current three months) because they're able to pull from the inventory supermarket.

8 Future State Vision

A conceptualized future state strategy like the one shown in Figure 37 is useful for gathering support among stakeholders. Given approval, the strategy is also useful as a roadmap to implement an actual pilot project solution – a requirement to demonstrate the strategy's capabilities and weaknesses. As the following sections describe, implementing a formal change in Amgen's current Enterprise Resource Planning (ERP) systems – SAP and a real-time, cloud-based interface called RapidResponse – requires a significant amount of resources like time, money and brainpower. In the interim, and as part of the pilot project, the team decided an Excel Macro tool that sources information directly from RapidResponse would best facilitate the dual inventory supermarket strategy. The following sections will describe the Excel macro model functions, and conclude with comments on the model's benefits, limitations and future enhancements.

8.1 Background: SAP and RapidResponse Infrastructure

Amgen began its adoption of an Enterprise Resource Planning (ERP) system made by SAP, a leading enterprise application software company, in 2005, taking the system live at Amgen in North America in April 2008. Today, SAP is used across all of Amgen's sites and functions, including Human Resources, Finance and Supply Chain. The company, like many other large corporations, adopted the system to reduce the risk of failure in various functions, support future growth and improve operational efficiency and effectiveness (May).

While Amgen employs SAP across the company and looks to it as its "single source for truth," the company has several other systems, some of which directly pull and / or push data to SAP. Manufacturing employs a Werum Manufacturing Execution System (MES), for example, which tracks and records manufacturing characteristics like material movements or weights of dispensed material. Additionally, in an effort to reduce its planning cycles and balance inventory levels while optimizing manufacturing capacity, Amgen's Supply Chain adopted Kinaxis's RapidResponse system. The real-time, cloud-based supply chain tool allows Amgen to rapidly manage supply chain details through collaboration across its various sites, as well as make both short-term planning decisions and long-term, strategic decisions.

8.2 Manufacturing Data Collection

The collection and analysis of supply chain and manufacturing data was critical to develop and support the future state vision. Supply chain data was primarily collected and analyzed at the corporate-level via the internship engagement, and was accessed through Amgen's ERP systems like SAP and RapidResponse. The bulk of the supply chain data used in the pilot project Excel macro tool revolves

around demand data (e.g., average demand, variability in demand), and is discussed earlier in this thesis, throughout Section 7: Pilot Project Product Selection.

Manufacturing data was primarily collected and analyzed at the site-level, and was managed by the lead Industrial Engineer for the project, as these were metrics regularly monitored by the Industrial Engineering organization to evaluate the site's performance. The manufacturing data required to support the pilot project's Excel macro tool revolved mainly around expected lead time and its variability. Product A's observed lead time is shown in Figure 38, which monitors these metrics in an I-MR chart from January 2011 to September 2011.

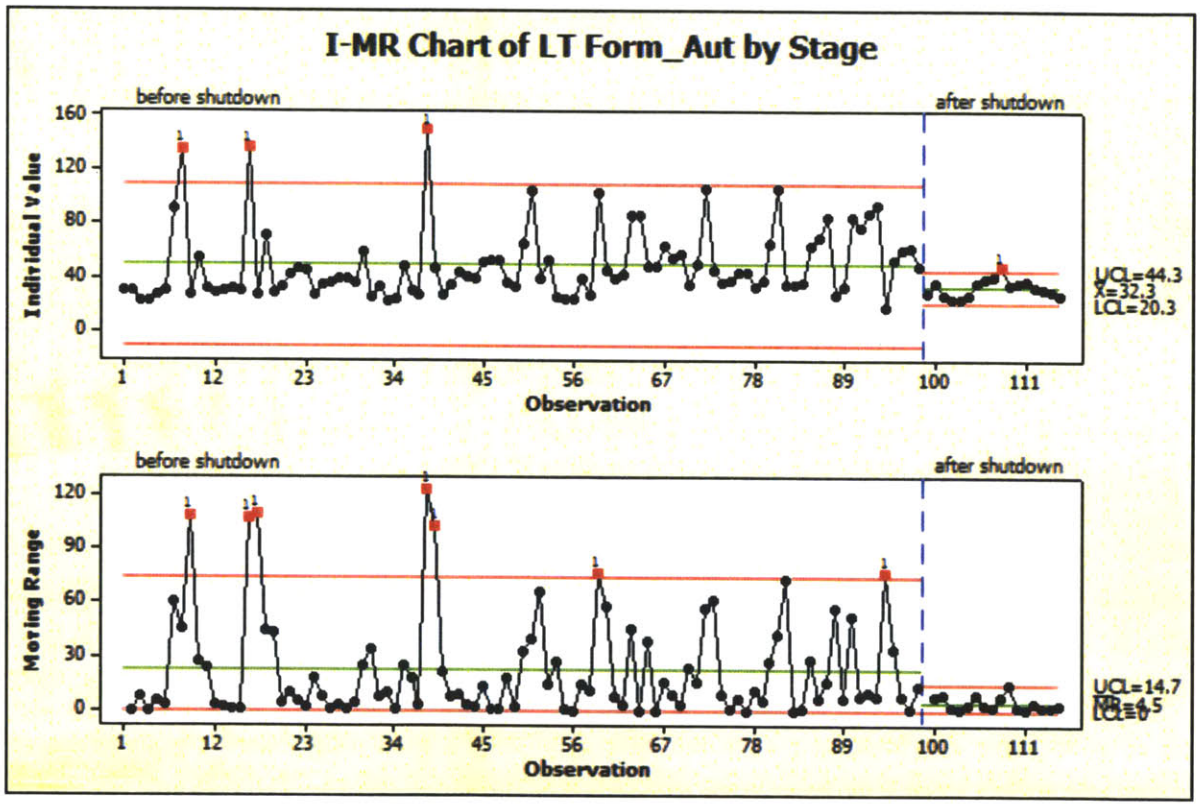


Figure 38 An I-MR control chart monitoring Product A's North American lead time (in calendar days) between the IDP (Inspected Drug Product) stage to product release, or when product can be shipped to the customer

Overall, the average lead time for a lot of North American Product A to move from the IDP stage to product release is 32.3 calendar days, or approximately a little more than one calendar month. This average lead time is somewhat skewed, however, by the fact that Amgen shuts down every year for one manufacturing week during the July 4 holiday. Manufacturing, however, does not shut down and instead works through its backlog of material, processing work in progress and unclogging the system so future

lots can move faster. As such, whereas the pre-shut down average lead time was 49 calendar days, a cleared backlog allowed manufacturing to operate with a 32.3 calendar days lead time throughout the remainder of the internship. These numbers were therefore used in the Excel macro, although continuous monitoring of these metrics allows the Excel macro users to input the most relevant lead time data.

8.3 Short-Term Solution: Proof of Concept Excel Macro Functionality

An inventory supermarket Excel macro was originally targeted as a proof of concept tool that would facilitate the inventory supermarkets short-term, and serve as a stepping stone for the company to develop a longer-term, more sustainable solution. Specifically, the Excel macro assists planners in performing the following tasks:

1. Import unaltered data directly from RapidResponse to:
    - Consolidate demand data into two pre-determined "supermarket buckets":
        - Supermarket #1: International Markets
        - Supermarket #2: Emerging Markets
    - Consolidate on-hand data into IDP SKU buckets
2. Calculate appropriate re-order point (ROP) level guidelines for the supermarket buckets, and corresponding months forward coverage (MFC) guidelines to satisfy forecast demand
3. Determine a guideline regarding whether manufacturing must produce IDP depending on the supermarket ROP level and the on-hand inventory

The Excel macro is built based on the assumption that the RapidResponse data will not change its format (i.e., column D always features the name of the country, column M always holds released on-hand inventory quantities, etc). After the on-hand supply and demand data are loaded and the assumptions are verified, the Excel macro pushes the information through various equations on the several tabs, as shown in Figure 39, and ultimately provides a recommendation as to whether or not certain material should be produced. The following sections will describe each tab in the Excel macro spreadsheet in detail.

Figure 39 The inventory supermarket Excel macro features several tabs that perform various calculations to ultimately recommend whether or not production should be turned on to refill a supermarket

The following sections will describe the functionality of the Excel macro, its benefits and limitations, and opportunities for improvement, especially for a long-term solution.

8.3.1 Tab #1: Control Panel

The power of the Excel macro is that it pulls unaltered demand and supply data directly from Amgen's real-time, cloud-based planning interface, RapidResponse, and automatically performs calculations not currently available to planners. To use the Excel macro, a planner, for instance, first downloads current Excel spreadsheet of Amgen's on-hand supply and demand data from RapidResponse to his / her desktop or a folder. As shown in Figure 40, the planner then loads the unaltered RapidResponse data directly into the Excel macro by pressing "Load Demand Data" or "Load On-Hand Data" located within the Inventory Supermarket Calculations Control Panel box, and selecting the appropriate spreadsheets that were previously saved. The Inventory Supermarket Calculations Control Panel is the macro portion, wherein Visual Basic code deletes old spreadsheet On-Hand and Demand data (from previous uses of the Excel macro) and pulls in new data. Each time new data is loaded, the "Last Updated" date updates to the current date to provide visibility into the calculations' relevancy.

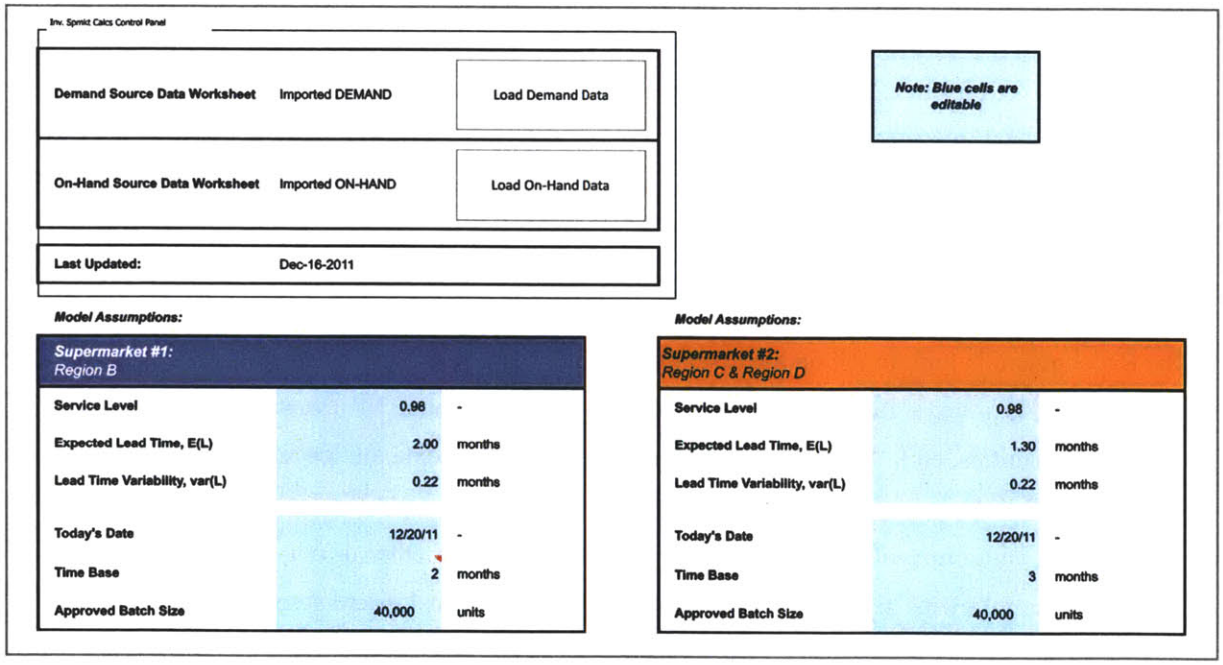


Figure 40 Snapshot of the inventory supermarket Excel macro Control Panel tab

Below the Inventory Supermarket Calculations Control Panel box are two boxes representing the assumptions used throughout the Excel macro for each inventory supermarket. Each supermarket assumption flow through the model independently, and can be adjusted independently according to current performance specifications, desired standards (e.g., service level), etc. Most of the assumptions currently loaded into the macro were provided by company standards, Industrial Engineering / Quality Engineering statistics or filings. For Region B, for instance, the following assumptions are employed:

- Service level is 98%
- Expected lead time is 2 months[25]
- Lead time variability is 0.22 months
- Approved batch size is 40,000 units

The remaining two boxes, "Today's Date" and "Time Base" are used throughout the Excel macro for calculations, per the following rules:

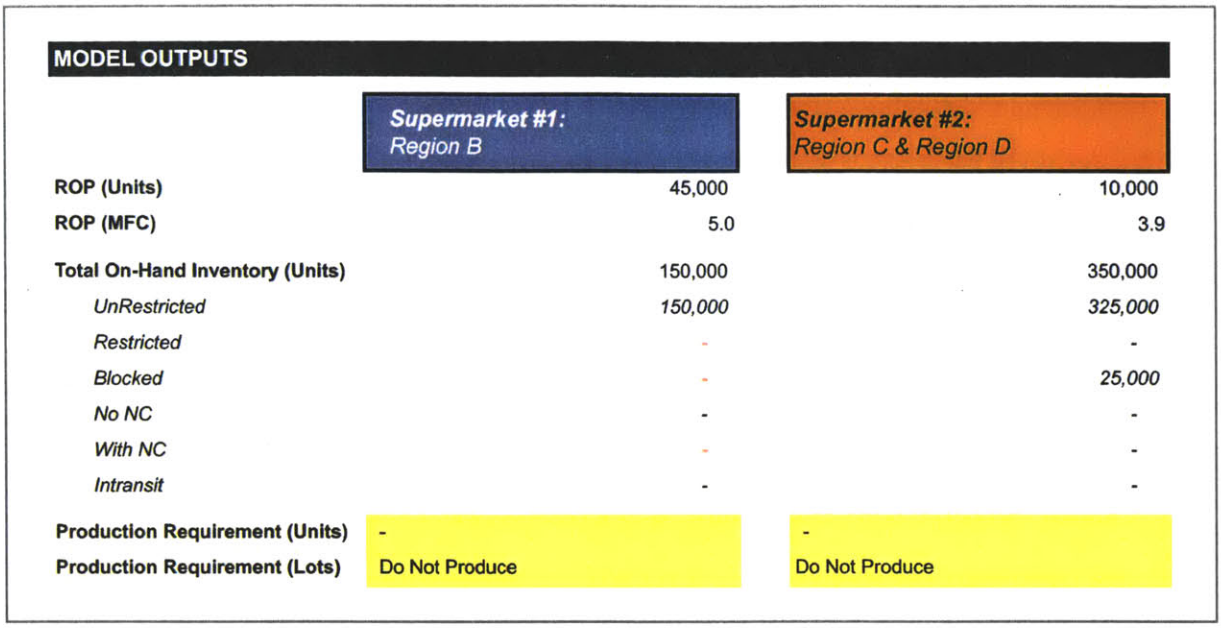
- "Today's Date" is used to determine remaining shelf life for materials, and will be explained in more detail in section 8.3.7: Tab #7: Aggregated Supply.
- "Time Base" is used to computer averages over monthly buckets, and will be explained in more detail in section 8.3.8: Tab #8: Supermarket Calculations.

8.3.2 Tab #2: Model Outputs

This tab is intended to be a "one stop shop," displaying the following outputs of the Excel macro calculations for each supermarket:

- Re-order point (ROP) in terms of units and months forward coverage (MFC).
- Total On-Hand Inventory in terms of units, per each stage as defined in RapidResponse (e.g., unrestricted, restricted, blocked, etc – these categories will be explained in further detail in section 8.3.7: Tab #7: Aggregated Supply).
- Production Requirements in terms of units and lots.

[25] Expected lead time and lead time variability are based on the average international lead time and lead time variability for products to move from the IDP stage to product release.



MODEL OUTPUTS

	Supermarket #1: Region B	Supermarket #2: Region C & Region D
ROP (Units)	45,000	10,000
ROP (MFC)	5.0	3.9
Total On-Hand Inventory (Units)	150,000	350,000
UnRestricted	*150,000*	*325,000*
Restricted	-	-
Blocked	-	*25,000*
No NC	-	-
With NC	-	-
Intransit	-	-
Production Requirement (Units)	-	-
Production Requirement (Lots)	Do Not Produce	Do Not Produce

Figure 41 Snapshot of the inventory supermarket Excel macro Model Outputs tab (numbers are fabricated and do not represent actual demand / on-hand supply data)

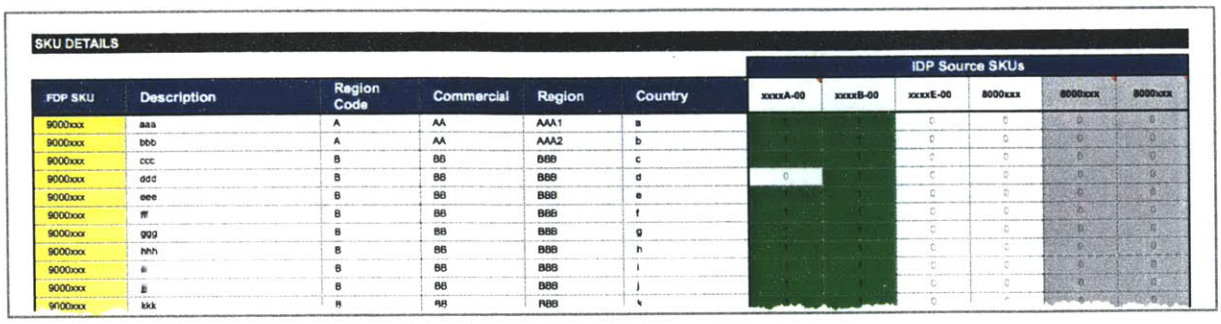
As shown in Figure 41, the Production Requirements category returns a zero (i.e., "-") if the Total On-Hand Inventory is greater than the ROP Requirement. In other words, production does not need to produce this material because there is enough material on-hand to satisfy demand and buffer against any expected volatility. Conversely, if the Total On-Hand Inventory level is less than the ROP Requirement, the output will display the balance of the Total On-Hand Inventory minus the ROP Requirement for that bucket (i.e., what must be produced to fulfill the inventory supermarket up to the ROP as defined).

The calculations use the Total On-Hand Inventory, which may be a combination of UnRestricted Inventory (i.e., completely released material ready for distribution), With NC material (i.e., material held by Quality for a nonconformance), or another listed category. Given the large amount of material on-hand (3.9+ MFC, or Months Forward Coverage), and the fact that a nonconformance is generally resolved within 90 days, it was believed that all material would eventually be available for use and so production shouldn't be turned on to over-produce to compensate for held material.

8.3.3 Tab #3: SKU Details

This tab currently doesn't play into the Excel macro functionality. Instead, this tab serves strictly as a reference repository for planners to organize which IDP SKUs can be used to create FDP SKUs. For each FDP SKU, a "1" is placed within the cell under an IDP SKU column if the FDP SKU can source from the IDP SKU; conversely, a "0" is placed in the cell if the FDP SKU cannot source from the IDP SKU. As

shown in Figure 42, this matrix can be used as a quick reference to understand material classifications rather than analyzing individual Manufacturing Bill of Materials (MBOMs) through SAP.



SKU DETAILS

FDP SKU	Description	Region Code	Commercial	Region	Country	IDP Source SKUs					
						xxxxA-00	xxxxB-00	xxxxE-00	8000xxx	8000xxx	8000xxx
9000xxx	aaa	A	AA	AAA1	a						
9000xxx	bbb	A	AA	AAA2	b						
9000xxx	ccc	B	BB	BBB	c						
9000xxx	ddd	B	BB	BBB	d	0					
9000xxx	eee	B	BB	BBB	e						
9000xxx	fff	B	BB	BBB	f						
9000xxx	ggg	B	BB	BBB	g						
9000xxx	hhh	B	BB	BBB	h						
9000xxx	iii	B	BB	BBB	i						
9000xxx	jjj	B	BB	BBB	j						
9000xxx	kkk	B	BB	BBB	k						

Figure 42 Snapshot of the inventory supermarket Excel macro SKU Details tab

It is firmly believed that MBOMs should always be referenced to confirm products are correctly sourcing material upstream for the intended downstream customer. However, as a next step, this tab could be used in an optimization model to understand the optimal inventory levels of each IDP SKU relative to each of the FDP SKU demand levels, and the sourcing / MBOM constraints around it.

8.3.4 Tab #4: Imported Demand

This tab is the imported RapidResponse actual demand data, which is imported when the planner clicks the "Load Demand Data" button in the Control Panel tab. This spreadsheet contents are protected per Visual Basic code in the Excel Macro so the user cannot change the system-reported demand data. A snapshot of this tab is not provided as it contains proprietary Amgen demand data.

8.3.5 Tab #5: Imported On-Hand

This tab is the imported RapidResponse actual on-hand supply data (i.e., on-hand stock of DS, DP, IDP, etc), which is imported when the planner clicks the "Load On-Hand Data" button in the Control Panel tab. The spreadsheet contents are protected per Visual Basic code in the Excel Macro so the user cannot change the system-reported on-hand supply data. A snapshot of this tab is not provided as it contains proprietary Amgen on-hand supply data.

8.3.6 Tab #6: Aggregated Demand

This tab sources data from the "Imported Demand" tab. For the "Summed Demand per Region" section shown in Figure 43, the spreadsheet consolidates an extensive list of RapidResponse demand data into predetermined supermarket buckets according to the following criteria:

- The region defined in each row (e.g., "Region C")
- The month defined in each column of the demand data (e.g., "11/01/11")
- Only low-volume syringes (e.g., "LVS") – *vials were not considered for the initial pilot project*

AGGREGATED DEMAND

	Month	11/01/11	12/01/11	01/01/12	02/01/12	03/01/12	04/01/12	05/01/12	06/01/12	07/01/12	08/01/12
	Count	1	2	3	4	5	6	7	8	9	10
Summed Demand *Per Region*											
Region A1		3,000	3,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	3,000
Region A2		25,000	25,000	25,000	25,000	25,000	25,000	25,000	25,000	25,000	30,000
Region C		250	750	500	1,500	1,500	500	1,500	2,500	1,000	1,000
Region B		25,000	25,000	30,000	30,000	30,000	45,000	45,000	45,000	45,000	45,000
Placeholder Demand		-	-	-	-	-	-	-	-	-	-
No Region		-	7,500	-	5,000	7,500	-	1,000	20,000	-	1,000
Region D		-	-	-	100	200	200	300	300	400	500
Bucketed Demand *Per Supermarket*											
Region A *Region A1 & A2*		28,000	28,000	27,000	27,100	27,200	27,200	27,300	27,300	27,400	33,500
Supermarket #1 *Region B*		25,250	25,750	30,500	31,400	31,300	45,300	46,200	47,200	45,600	45,500
Supermarket #2 *Region C & D*		-	7,500	-	5,000	7,500	-	1,000	20,000	-	1,000

Figure 43 Snapshot of the inventory supermarket Excel macro Aggregated Demand tab (numbers are fabricated and do not represent actual demand data)

As an example: cell C10 (Region C, month 11/01/11) sums all demand defined as "Region C" found in the RapidResponse demand spreadsheet for the month corresponding to 11/01/11 (i.e., November), and only for LVSs. Cell D10 (Region C, month 12/01/11) does the same thing as previously described, but for the next month (i.e., December), and so on.

For the "Bucketed Demand per Supermarket" section, the spreadsheet sums the above "Summed Demand per Region" rows in the appropriate pre-determined supermarket buckets, per month.

As an example: cell C18 (Region A, month 11/01/11) sums demand from Region A1 and Region A2 for the first month, and only for LVSs. Cell D18 does the same thing, but for the next month, and so on.

8.3.7 Tab #7: Aggregated Supply

This tab sources data from the "Imported On-Hand" tab. For each of the on-hand supply classifications (UnRestricted, Restricted, Blocked, etc) shown in Figure 44, the spreadsheet consolidates an extensive list of RapidResponse on-hand supply data according to the following criteria:

- The on-hand supply classification (e.g., "UnRestricted")
- The IDP SKU (e.g., "xxxxA-00")
- The remaining shelf-life category, explained in more detail below

AGGREGATED SUPPLY: ON-HAND INVENTORY

Note: Blue cells are editable

		xxxxA-00	xxxxxB-00	xxxxxE-00	800xxxx	800xxxx	800xxxx
		DS Site 3	*DS Site 4*	*DS Site 1*	*Region B-Only (old)*	*Region A-Only*	*Region B-Only (new)*
Shelf-Life Limit (days)		90	90	90	90	90	90
UnRestricted	*Released by Quality, ready to use*	1,000	25,000	125,000	325,000	50,000	150,000
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		*1,000*	*25,000*	*125,000*	*325,000*	*50,000*	*150,000*
Restricted	*NA - not able to use, restricted by Quality*	-	-	-	-	-	-
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		-	-	-	-	-	-
Blocked	*NA - not able to use, restricted by Quality*	-	-	-	3,000	-	-
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		-	-	-	*3,000*	-	-
No NC	*Inventory "in work" at Quality release stage*	-	-	-	-	-	40,000
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		-	-	-	-	-	*40,000*
With NC	*Inventory held by Quality due to an NC*	-	-	-	-	-	75,000
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		-	-	-	-	-	*75,000*
Intransit	*Material in-transit to "customer," or next user*	-	-	-	-	-	-
Age < SL Limit		-	-	-	-	-	-
Age > SL Limit		-	-	-	-	-	-
Total	*Total*	1,000	25,000	125,000	328,000	50,000	265,000

Figure 44 Snapshot of the inventory supermarket Excel macro Aggregated Supply tab (numbers are fabricated and do not represent actual demand data)

Remaining shelf-life is an important consideration and constraint for supply and demand planning, as was described in section 6.3.4: Remaining Shelf Life. As such, the Excel macro classifies IDP on-hand data into two buckets depending on the manufacturing date: (1) material that was manufactured less than 90 days ago, and (2) material that was manufactured more than 90 days ago. The light blue cells under each

of the IDP SKUs can be edited, depending on the desired shelf-life. For instance, if these cells are set at "90" (meaning, 90 days), each type of IDP inventory per SKU will be broken up into two segments:

- **Age < SL Limit:** Quantity of material that was manufactured less than 90 days ago, and is thus "freshest."
- **Age > SL Limit:** Quantity of material that was manufactured greater than 90 days ago, and is thus "older."

To determine the number of days that inventory has been sitting on the shelf, the Excel macro looks at the following data:

- The blue, editable "Shelf-Life Limit (days)" cells, which are set this to whatever the planner desires to monitor. The metric "90 days" was originally entered, since many emerging markets and several other international regions have very high remaining shelf-life requirements, so material balances per this restrictive constraint appeared useful.
- The manufacturing date stored per batch, which comes from RapidResponse and is sourced from the "Imported On-Hand" tab.
- The "Today's Date" data located on the "Control Panel" tab.
- The on-hand inventory classification (e.g., "UnRestricted").
- The IDP SKU (e.g., "xxxxA-00").

As an example: for each on-hand supply classification and each IPD SKUs, this spreadsheet looks in the RapidResponse on-hand supply data for this specified on-hand inventory classification and IDP SKU. It then analyzes the following:

RapidResponse Manufacturing Date $\geq$ *Today's Date – Shelf-Life Limit (days)*

In other words, the spreadsheet looks at the corresponding manufacturing date for the specified material, as supplied by RapidResponse, and if this date is greater than or equal to the difference between "Today's Date" and the "Shelf-Life Limit (days)," the material is classified as "Age < SL Limit" material.

Conversely, the following classifies material as "Age > SL Limit" material:

RapidResponse Manufacturing Date < Today's Date – Shelf-Life Limit (days)

8.3.8 Tab #8: Supermarket Calculations

This tab performs all the supermarket calculations that are ultimately summarized on tab #2: Model Outputs. As the top of this spreadsheet, shown in Figure 45, there are three categories that facilitate many of the following calculations throughout the spreadsheet:

- **Month:** This month count is simply a count that other calculations are based on. Each column corresponds with a month in the imported RapidResponse demand and on-hand data (e.g., the first month listed in the RapidResponse data file is always labeled month "1"). This count never changes.
- **Month Count:** On the "Control Panel" tab, the user can enter a "Time Base," or the number of months to "look ahead" to perform calculations such as averages over a number of specified months.

  For example: If the "Control Panel" tab's "Time Base" reads "3," this means that average demand will be taken over three months (average is taken using data from the current month (e.g., November) + data from two months ahead of the current month (e.g., December and the following January).

  A time base of two months was originally selected for Supermarket #1 because the manufacturing site that serves this region has a lead time of two months. A time base of three months was originally selected for Supermarket #2 because orders are placed by emerging market customers on a quarterly basis, so demand was amortized over this time period, as well. This strategy provides a balanced plan to manufacturing over time without compromising remaining shelf-life.

- **Column Count:** Depending on the "Time Base" entered in the "Control Panel" for each supermarket, this updates the column ahead "x" number of months (or the number entered in the "Time Base" cells). This "Column Count" is used to calculate "Std Dev of Demand, sigma_D" over the time base desired.

  For example: if the "Control Panel" tab's Supermarket #2 "Time Base" cell reads "3," this means that Supermarket #2 Column Count cell D7 will read "F," since column F is the third column away from the current column (i.e., when counting: column D = 1, column E = 2, column F = 3).

SUPERMARKET CALCULATIONS

	Month	1	2	3	4	5	6
Supermarket #1	Month Count	0	2	4	6	8	10
	Column Count	E	F	G	H	I	J
Supermarket #2	Month Count	1	4	7	10	13	16
	Column Count	F	G	H	I	J	K
Supermarket #1 *Region B*	Time Period Demand	25,000	50,000	75,000	100,000	100,000	50,000
	Avg Monthly Demand, E(D)	12,500	25,000	37,500	50,000	50,000	25,000
	Avg Monthly Demand over LT, E(X)	25,000	50,000	75,000	100,000	100,000	50,000
	Std Dev of Demand, sigma_D	10,000	10,000	10,000	-	10,000	
	Combined Std Dev, sigma_x	18,875	28,723	40,078	50,000	51,962	
	Safety Stock	38,764	58,989	82,310	102,687	106,716	
	Re-Order Point	63,764	108,989	157,310	202,687	206,716	
	MFC	5.1	4.4	4.2	4.1	4.1	
Supermarket #2 *Region C & Region D*	Time Period Demand	7,500	12,500	21,000	1,000	-	-
	Avg Monthly Demand, E(D)	2,500	4,167	7,000	333	-	-
	Avg Monthly Demand over LT, E(X)	3,250	5,417	9,100	433	-	-
	Std Dev of Demand, sigma_D	2,500	5,000	5,000	-	-	
	Combined Std Dev, sigma_x	3,791	7,061	9,028	333	0	
	Safety Stock	7,787	14,502	18,541	684	0	
	Re-Order Point	11,037	19,920	27,641	1,117	0	
	MFC	4.4	4.8	3.9	3.4	-	

Figure 45 Snapshot of the inventory supermarket Excel macro Supermarket Calculations tab (numbers are fabricated and do not represent actual demand data)

Once the infrastructure of this spreadsheet is established via month and column counts, the following calculations are performed:

- **Time Period Demand:** This is the sum of demand over the number of months defined in the "Time Base" cells in the Control Panel.
- **Avg Monthly Demand, E(D):** This is Time Period Demand divided by the number of months in the "Time Base."
- **Avg Monthly Demand over LT, E(X):** This is the Avg. Monthly Demand multiplied by the lead time defined in the "Expected Lead Time, E(L)" cells in the Control Panel.

- **Std Dev of Demand, sigma_D:** This is the standard deviation of demand over the number of months defined in the "Time Base" cells in the "Control Panel." (As mentioned previously, however, this calculation is performed using the "Column Count" cells.) This characteristic is calculated using the current month's demand and the following months' demand, up to the month corresponding to the column listed in the "Column Count."

  For example: as described above, if the "Control Panel" tab's Supermarket #2 "Time Base" cell reads "3," this means that Supermarket #2 Column Count cell D7 will read "F," since column F is the third column away from the current column. "Std Dev of Demand, sigma_D" is then calculated based on the demand for the supermarket in columns D – F, or over a three month horizon.

- **Combined Std Dev, sigma_x:** This is calculated per the following formula:

Equation 3 Combined Standard Deviation

$$\sigma_x = \sqrt{E(L)var(D) + E(D)^2 var(L)}$$

The use of this equation is one of two approaches suggested by Silver, et. al in their textbook *Inventory Management and Production Planning and Scheduling* when calculating re-order points for systems having variable replenishment lead time. This approach assumes that, within a unit time period, the lead time (L) and demand (D) are independent random variables. While this may be a reasonable approximation for reality, Silver recognizes that in some cases, high demand is positively correlated with long lead times (a heavier workload takes longer to produce) and likewise, low demand is negatively correlated with long lead times (due to waiting for sufficient work to accumulate to produce efficiently).

In Amgen's case, we see that high demand is often positively correlated with long lead times,. However, this is the case only to a point. As demonstrated in Section 5.1.4: Changeover Impact and Manufacturing System Design, low volume demand may also be positively correlated with long lead times as setup and closedown times consume the majority of the total run time.

For the purpose of the pilot project Excel macro, however, L and D were assumed to be independent random variables so that Equation 3 applied. In this case, σ_x represents the expected standard deviation of the total demand in a replenishment lead time. Within the unit time period, $E(L)$ is the expected lead time, $var(L)$ is the variability in lead time, $E(D)$ is the expected demand and $var(D)$ is the variability of demand. Ultimately, incorporating the uncertainty in L increases

the combined standard deviation, which ultimately increases the re-order point – an appropriate consideration to account for the variability not only in demand, but also in supply lead time (Silver, Pyke and Peterson).

Each of these variables is defined on either the Control Panel tab or tab #8: Supermarket Calculations, per month if applicable.

- **Safety Stock:** This is calculated per the following formula:

Equation 4 Safety Stock

$$SS = k\sigma_x$$

where k is called the safety factor and is calculated using the Excel function "normsinv" corresponding to the Service Level defined on the Control Panel tab. The combined standard deviation, σ_x, was calculated per month on the #8: Supermarket Calculations tab.

- **Re-Order Point:** This is calculated per the following formula:

Equation 5 Re-Order Point

$$ROP = E(X) + SS$$

This formula is used in a periodic-review, order-up-to-level *(R,S)* system, which is also known as a replenishment cycle system. This system is in common use, especially for items / products that share resources such as equipment or a supplier. This system was selected because once a month, Amgen performs its S&OP process, which is a suitable time, *R,* to review inventory levels, taking the appropriate actions to raise inventory to level *S* (Silver, Pyke and Peterson).

Each of these variables is defined on a monthly basis on the #8: Supermarket Calculations tab.

- **Months Forward Coverage (MFC):** This is calculated by dividing the Re-Order Point (ROP) by the Avg Monthly Demand, E(D), unless the Avg Monthly Demand, E(D) = 0 (in this case, a "-" is returned in the cell).

8.3.9 Tab #9: Improvements Log

A log of improvements for the inventory supermarket Excel macro is located on the last tab of the spreadsheet where issues to fix, questions to answer, etc are logged by date and include closure status and notes. This improvements log was maintained throughout the internship to ensure traceability within the macro revisions.

8.4 Model Benefits, Limitations and Future Enhancements

Developed as a pilot project, the inventory supermarket Excel macro serves just this purpose: it's merely a representation of a potential capability Amgen might choose to adopt. While the Excel macro is a powerful tool that consolidates a significant amount of information and provides alternative views not currently available in RapidResponse – for example, it provides data around re-order points and shelf-life – it is by no means a robust model that translates across Amgen's product lines. The value of the Excel macro is that it provides a common platform from which improvements can be made, and serves as a stepping-stone for future work in more established, network-wide systems such as SAP and RapidResponse.

One of the more successful interactions the Excel macro facilitated during the internship was with Amgen's Business Center of Excellence, which is in part responsible for the company's systems like SAP and RapidResponse. A small team of former planners, who now work to configure and enhance the company's ERP systems, used the Excel macro to understand the functionality required to support an inventory supermarket. The team was extremely supportive of the strategy behind inventory supermarkets, and appreciated the framework for its demonstration capabilities. Upon the conclusion of the internship, this team had adopted the strategy and established a 2012 goal to further the capabilities within the SAP / RapidResponse systems.

As a next step, the Excel macro could be improved by integrating optimization capabilities. As mentioned in section 8.3.3: Tab #3: SKU Details, a feature should be integrated that assists planners in optimally stocking and producing IDP inventory. As mentioned earlier, this capability currently does not exist, and so planners must verify which IDP SKUs specific FDP SKUs are able to source from. Similarly, planners must verify remaining shelf-life data of all in-stock inventory, as different regions require various products with differing remaining shelf-life. These verification steps are time consuming and error-prone processes that require planners to trace back through SAP MBOMs and manufacturing data to ensure their sourcing assumptions are correct – and this all happens before any actual planning takes place. Providing an optimization capability in either the Excel macro or in SAP / RapidResponse would not only streamline the planning process, but reduce the risk of delivering the wrong configuration of a product to a customer.

Furthermore, more statistical data could be incorporated into the Excel macro. To date, the macro assumes that a dedicated planner with judiciously seek out and update the Excel macro with relevant lead time and variability data; however, this may not be a realistic assumption given a typical Amgen

employee's demanding work schedule. Automatically incorporated, up-to-date data would significantly improve the credibility of this model if used on an ongoing basis.

Lastly, in his book *High-Mix Low-Volume Manufacturing*, R. Michael Mahoney adamantly states that successful high-mix low-volume manufacturing environments are not merely the result of thorough analysis and strategic design, but rather due to individually successful managers who lead according to clearly defined future state visions. Amgen has extremely talented employees from both technical and managerial backgrounds that are capable of understanding and leading Amgen's transformation to high-mix low-volume manufacturing and planning.

One transformation Amgen must manage on its high-mix low-volume transformation journey is the adoption of the Excel macro's demonstrated capabilities by Amgen's ERP systems. As the company expands globally and complexity inherently increases, the planning systems must keep pace and provide the appropriate infrastructure and controls for the many constraints facing the industry and the company.

9 Conclusions and Future Work Recommendations

As Amgen increases its global footprint, it faces a number of operational challenges where "one size fits all" manufacturing and planning systems no longer support the future demand profile. Today's product demand suggests two distinct market segments: the High-Volume, Low-Mix (HVLM) segment that Amgen currently serves, and the emerging High-Mix, Low-Volume (HMLV) segment that is rapidly increasing SKU complexity. To compete in the global marketplace, Amgen must manage – and capitalize on – this market segmentation.

The strategy described in this thesis addressees the two major HMLV challenges Amgen faces with international expansion:

1. Limited demand responsiveness due to a three month Fill / Finish manufacturing lead time
2. Increased changeover impact and scrap risk due to low-volume requirements

The thesis proposes a dual-inventory supermarket strategy with a supporting Excel macro tool that is believed to mitigate the above two major challenges, with the following results:

- Decreases Fill / Finish manufacturing lead time to approximately one month
- Provides a buffer against supply chain variability
- Improves demand signaling
- Sustains on-time deliveries

Beyond identifying and proposing strategies to mitigate the challenges Amgen faces with global expansion, there are additional considerations Global Supply Chain might analyze (perhaps with an MIT LGO intern) to further complement its HMLV strategy.

- **SKU Management:** A process to minimize SKU complexity as Amgen expands internationally will streamline Amgen's supply chain, despite added volume and distribution networks. A team should ultimately manage SKU proliferation, making business case recommendations about discontinuing SKUs, consolidate SKUs and adding new SKUs when Amgen enters new markets. The team should champion universality (i.e., common dosages, packaging, SKUs) over the current model of specialization.
- **Expiry / Remaining Shelf-Life:** Amgen can simplify its planning process by standardizing the remaining shelf-life options it offers customers. Instead of offering customers their choice of remaining shelf-life, the company should capitalize on its HMLV and HVLM market segment manufacturing capabilities and offer only one or two (instead of several) shelf-life option for each

segment. Minimizing the remaining shelf-life options will remove a portion of this addition complexity layer when planning for entire product lines.

- **Duplicate Testing Strategy:** Amgen can improve its supply chain flexibility by implementing a duplicate testing strategy. By testing all material in the same way – that is, to the same specifications and in the same locations – Amgen will be better equipped to satisfy volatile, low-volume demand quickly and with the freshest material possible, will still satisfying high-volume market demand.
- **On-Demand Printing, and Other Disruptive Strategies:** With global expansion and increasing downstream complexity in Amgen's manufacturing process, the company should place a premium on "thinking outside the box" to generate disruptive strategies to optimize its supply chain. For instance, on-demand printing pushes differentiation as far downstream as possible: to the distribution center. In this case, nude vials might be shipped to Amgen's various distribution centers, where products are labeled right before distribution. While this strategy poses many risks for the company, it also promotes supply chain flexibility. An effort to explore strategies that potentially transform the entire supply chain should be explored as aggressively as the company is increasing its global footprint.

10 Glossary

AML **Amgen Manufacturing Limited**, or Amgen's Puerto Rico manufacturing facility.

CHO **Chinese Hamster Ovary**, or a cell line that is usually used to create human therapeutics because they are generally regarded as safe (GRAS), synthesize proteins in a similar way that humans do, and are able to grow and produce product forever.

DMAIC **Define – Measure – Analyze – Improve – Control**, or an acronym representing a data-driven Six Sigma improvement methodology.

DP **Drug Product**, or the stage in the manufacturing process that represents Drug Substance (DS) filled into a presentation, or container such as a vial or pre-filled syringe.

DS **Drug Substance**, or the stage in the manufacturing process that represents a scaled up, purified and filtered drug held in a cryovessel or carboy.

ERP **Enterprise Resource Planning**, or a software system that integrates many sources of enterprise information such as finance / accounting, manufacturing, sales, etc data intended to aid management in cross-organizational planning and decision-making.

FDA **Food and Drug Administration**, or an agency of the United States Department of Health and Human Services, which regulates many parts of the biopharmaceutical industry's processes, from marketing to manufacturing.

FDP **Final Drug Product**, or the stage in the manufacturing process that represents a filled, inspected, labeled, packaged and ready-to-ship drug intended for a customer.

GRAS **Generally Regarded As Safe**, or acronym defined by the FDA that requires all substances such as biopharmaceuticals to be safe for their specified, intended use.

ICO **International Commercial Operations**, or part of Amgen's Operations organization that manages commercial demand for international countries (i.e., not North American countries).

IDP **Inspected Drug Product**, or the stage in the manufacturing process that represents an inspected Drug Product (DP).

LDP **Labeled Drug Product**, or the stage in the manufacturing process that represents an inspected and labeled Drug Product (DP).

MBOM **Manufacturing Bill of Material**, or the list of required parts (or chemicals, for instance) and their corresponding quantities (or amounts, for instance) required to create an assembly (or drug, for instance).

MCB **Master Cell Bank**, or a reserve of cells from a desired cell line that are used only when absolutely necessary.

MES **Manufacturing Execution System**, or an information software system used to manage – and sometimes optimize – manufacturing operations in a factory or factories.

MFC **Months Forward Coverage**, or the number of months a certain level of inventory can cover at any point in time. In other words, it is the current inventory divided by the average monthly demand.

NACO **North American Commercial Operations**, or part of Amgen's Operations organization that manages commercial demand for North American countries.

PFS **Pre-Filled Syringe**, or a presentation format that includes a syringe barrel (plastic or glass) filled with Drug Product (DP), a plunger and a needle to transfer the DP to the patient.

ROP **Re-Order Point**, or a predetermined, specified level of inventory that, when reached, triggers a process that triggers production to produce additional inventory to refill the level.

RSL **Remaining Shelf Life**, or the amount of time left before a therapeutic expires and is no longer considered safe for human consumption.

WCB **Working Cell Bank**, or a reserve of cells from a desired cell line that were derived from the Master Cell Bank (MCB) and are used to produce products during scale-up.

11 Bibliography

American Society for Quality. Organization-Wide Approaches. 2012 йил 1-January. 2012 йил 14-January <http://asq.org/learn-about-quality/six-sigma/overview/dmaic.html>.

Amgen, Inc. About Amgen. 2011 йил 7-August <https://myamgen.amgen.com/aboutamgen/Pages/AboutAmgen.aspx>.

—. "Amgen 2010 Annual Report and Financial Summary." Annual Report. 2011.

—. "Amgen Manufacturing." 2011 йил 17-November. Amgen Manufacturing. 2012 йил 14-January <http://www.amgen.com/pdfs/Fact_Sheet_Manufacturing.pdf>.

—. "Amgen, Inc. 10-K." 10-K. 2005.

—. "An Introduction to Biotechnology." 2009 йил 1-September. An Introduction to Biotechnology. 2011 йил 1-July <http://www.amgen.com/pdfs/misc/An_Introduction_Biotechnology.pdf>.

—. Operational Safety Stock (OSS) Documentation. Report. Amgen, Inc. Thousand Oaks, 2011.

—. Pipeline. 2011 йил 9-February. 2012 йил 17-January <http://www.amgen.com/science/pipe.html>.

Binder, Gordon and Philip Bashe. Science Lessons. Boston: Harvard Business Press, 2008.

Buzzard, J., et al. US healthcare reform: A legislative pathway for biosimilars will spur growth - and present new challenges. Report. McKinsey & Company. New York: McKinsey & Company, 2010.

Carroll, John S. Introduction to Organizational Analysis: The Three Lenses. Report. Massachusetts Institute of Technology. Cambridge, 2006.

Coombs, Clyde F. Printed Circuits Handbook. Columbus: McGraw-Hill Professional, 2007.

Ebel, Thomas, et al. The value of flexibility: Pharma supply chain 2020. Report. McKinsey & Company. Dusseldorf: McKinsey & Company, 2010.

Ernst & Young. Beyond borders: Global biotechnology report 2011. Annual Report. Ernsy & Young. New York City: EYGM Limited, 2011.

IBISWorld. L6724-GL - Global Biotechnology - Global Industry Report. 2011 йил 14-September. IBISWorld. 2012 йил 17-January <http://clients.ibisworld.com.libproxy.mit.edu/globalindustry/keyfactors.aspx?indid=2010>.

LexisNexis. Company Reports. 2012 йил 1-January. 2012 йил 17-January <http://www.lexisnexis.com.libproxy.mit.edu/hottopics/lnacademic/?shr=t&sfi=AC02NBCmpDosSrch>.

Mahoney, R. MIchael. High-Mix Low-Volume Manufacturing. Upper Saddle River: Prentice Hall PTC, 1997.

May, Pamela. "Enabling Growth and Innovation in the Biotechnology Industry." SAPPHIRE 2009 Orlando Online. Orlando, 2009 йил 14-May.

Miltenburg, John. Manufacturing Strategy: How to Formulate and Implement a Winning Plan. New York: Productivity Press, 2005.

Mu Sigma. About Us. 2011 йил 1-January. 2012 йил 14-January <http://www.mu-sigma.com/aboutus/aboutus-whoweare.html>.

Naughton, Alyson B. Aligning Tool Set Metrics for Operations in a Multi Technology High Mix Low Volume Manufacturing Environment. Cambridge: Massachusetts Institute of Technology, 2005.

Naylor, J Ben, Mohamed N Main and Danny Berry. "Leagility: Integrating the lean and agile manufacturing paradigms in the total supply chain." International Journal of Production Economics (1999): 107-118.

Next Generation Pharma. "Staying Power." Next Generation Pharma 2010 йил 23-June: 86-89.

Olavson, Thomas, Hau Lee and Gavin DeNyse. "A Portfolio Approach to Supply Chain Design." Supply Chain Management Review 2010.

OneSource. "Amgen, Inc." Company Profile. 2012.

Pagh, Janus D. and Martha C. Cooper. "Supply Chain Postponement and Speculation Strategies: How to Choose the Right Strategy." 19.2 (1998).

Reichhart, A. and M. Holweg. Creating the Customer-responsive Supply Chain: A Reconciliation of Concept. Working Paper. Judge Business School, University of Cambridge. Cambridge, 2005.

Reichhart, Andreas, Jose M. Framinan and Matthias Holweg. "The role of inventory in enabling supply chain responsiveness." Information Control Problems in Manufacturing 12.1 (2006).

Silver, Edward A., David F. Pyke and Rein Peterson. Inventory Management and Production Planning and Scheduling. John Wiley & Sons, 1998.

Silver, Steven. Sector Scorecard: GICS Sub-Industry Summary. 2011 йил 22-November. Standard & Poor's. 2011 йил 22-Novermber <http://solutions.standardandpoors.com/SP/sectortool/subIndustrySummary.do?contentId=WS-

Soman, C.A., D.P. Van Donk and G. J. C. Gaalman. "A basic period approach to the economic lot scheduling problem with shelf life considerations." International Journal of Production Research 42.8 (2004): 1677-1689.

The Boston Globe. "Making a Biotech Drug." The Boston Globe 2007 йил 29-July.

Torres, Eduardo, Vishal Khanderia and Sally Smith. High-Mix Low-Volume (HMLV) Strategy for Amgen Operations. Amgen, Inc. Thousand Oaks, 2011.

Wong, Hartanto, Andrew Potter and Mohamed Naim. "Evaluation of Postponement in the Soluble Coffee Supply Chain: A Case Study." International Journal of Production Economics 131 (2011): 355-364.

Yang, Kai and Basem El-Haik. Design for Six Sigma: A Roadmap for Product Development. New York: McGraw-Hill, 2003.

Ziegler, Marco, Ulf Schrader and Thomas Ebel. "Supply Chain Yoga." Pharmaceutical Manufacturing Magazine 2010 йил 8-November.