Allocation Strategy for Production Network Designed to Mitigate Risk

by

Roy J. Lehman, III

B.S.E. Civil Engineering Systems, University of Pennsylvania, Philadelphia, 2004
B.A. Urban Studies, University of Pennsylvania, Philadelphia, 2004

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 2011

Signature of Author _____
May 6, 2011
Engineering Systems Division, MIT Sloan School of Management

Certified by _____
Donald B. Rosenfield, Thesis Supervisor
Director, Leaders for Global Operations Program
Senior Lecturer, MIT Sloan School of Management

Certified by _____
David Simchi-Levi, Thesis Supervisor
Co-Director, Leaders for Global Operations Program
Professor of Civil and Environmental Engineering, MIT

Accepted by _____
Nancy Leveson, Chair, Engineering Systems Division Education Committee
Professor, Aeronautics and Astronautics and Engineering Systems Division

Accepted by _____
Debbie Berechman, Executive Director of MBA Program
MIT Sloan School of Management

Efficient Product Allocation Strategy to Enable Network-Wide Risk Mitigation

by

R.J. Lehman III

Submitted to the MIT Sloan School of Management and the Engineering Systems Division on May 6, 2011 in Partial Fulfillment of the Requirements for the Degrees of Master of Business Administration and Master of Science in Engineering Systems

Abstract

Amgen Inc. currently manufactures, formulates and fills substantially all of their global drug product units in a single primary facility ("Site 1A"). Concerned about the inherent risks posed by the geographic concentration of these activities, Amgen has decided to acquire a new international Risk Mitigation Site ("RMS"), expand existing bulk manufacturing infrastructure at Site 1A, and construct a new formulation and filling facility colocated with Site 1A ("Site 1B").

Bringing both sites online in the near future will create a novel operational challenge for Amgen, as it will present a broad range of formulation/fill production allocation decisions that did not previously exist. If per-unit costs (production, logistics, etc.) were considered to be typically higher at either RMS or Site 1A/B, an unconstrained optimization model might suggest filling/finishing all product at whichever site has the lowest average cost. However, we assume that RMS should be able to ramp up to full capacity within 3 months of an adverse occurrence at Site 1A. This translates to a minimum product flow constraint through RMS, irrespective of per unit costs, that will keep the facility sufficiently staffed to prepare for a fast ramp-up. Furthermore, helping Amgen mitigate the risks of geographic concentration, RMS may typically produce only a portion of global demand for any product.

Given this situation, this thesis develops a product allocation strategy that will:
1) minimize the financial cost of filling various quantities of drug product at the new facility, yet
2) maintain at RMS the expertise required begin manufacturing all drugs in a short period of time.

A mixed-integer linear program ("MILP") was developed to capture variable costs of the formulation & fill process for each drug product ("DP") and market combination. The objective of this model is to minimize total supply chain costs subject to meeting market demand and maintaining a sufficient amount of product flow through the RMS facility. The analysis assumes that the decision to develop fill capacity at both RMS and Site 1B is complete and that both facilities will be licensed to fill all products that currently run through Site 1A (i.e. capital investment decisions will not be analyzed in this study).

The outcome of this study is a product allocation strategy that minimizes network costs as well as a tool that will enable Amgen to solve for minimal network costs under additional future scenarios.

Thesis Supervisor: Donald B. Rosenfield
Title: Senior Lecturer, MIT Sloan School of Management

Thesis Supervisor: David Simchi-Levi
Title: Professor of Civil and Environmental Engineering, MIT

This page intentionally left blank.

Acknowledgments

This thesis would not have been possible without the time and thoughtful contributions of many individuals over the past nine months. First and foremost, I would like to thank my advisors, Don Rosenfield and David Simchi-Levi. Their insights and participation in this project, including several key on-site meetings with Don, were invaluable in shaping this study and resolving numerous challenges along the way. Veterans of the LGO Program, Leigh Hunnicutt and Julie Matthew provided assistance and perspective that positively contributed to both my experience at Amgen as well as this work.

Working alongside the Operations and Strategic Planning group ("OSP") within Amgen was truly an unparalleled experience, and I am very appreciative of the time I had with this group and the significant support provided by its members. Rayne Waller and Bill Rich were most supportive sponsors. Som Chattopadhyay provided great insights and direction throughout the development of this project. Lisa Correia was extremely supportive of my work, essential to scoping the project, and invaluable in connecting me to key people throughout Amgen. Majed Kheir made useful contributions toward multiple parts of this project and related work. Peter Pick provided unique and helpful insights into the research approach and developed the capacity model on which many of the assumptions on this research relied. Innumerous thanks to Amy Imbrogno for tirelessly keeping such a dynamic and high-performing team so well organized.

I also greatly appreciate the positive impact that many other individuals from within OSP and across Amgen had on this project and other work during my time there. These people include: Bill Keefe, Roshni Dasgupta and Naren Kadaba (OSP), David Yapp, Francine Ryan, Andrea Romoli, Ricardo Diaz, Chris Atwell and Morgan Booth (Finance), Eduardo Torres (Supply Chain), Elisabeth Kaszas, Andrew Mica, Kris Lee, Jim Chan, Uel Leite, Kenny Craig, Yvette Holmes, Chong-Im Kim and Vishal Kanderia (Commercial Manufacturing), Gary Hutchinson, Rosemarie Dolatre and Kelley Van Arsdale (Transportation), all from Thousand Oaks; Ingrid Berglund and Pat Woods from Louisville Distribution Center; Martijn van den Berg, Maarten Denneman, Danielle Kooij and Alexander van der Lee, Esteban Santos, Eduardo Janer, Enid Miranda and Darcy Rosado from additional sites.

Aside from the support of my advisors and many team members at Amgen, west coast LGO camaraderie with Ben Wheeler and Noramay Cadena greatly added to the experience of living there.

Although education, guidance, teamwork and appropriate resources are all important to the completion of a project of this scale and complexity, a supportive base of personal connections is absolutely essential. I regularly rely on I-Fong's constant support, understanding, patience and humor. I am pleased to report that she has recently agreed to marry me and will continue ad infinitum to surpass me in beauty, intelligence and charm. In addition, I continue to be immensely grateful for the unshakeable foundation that my parents, Roy and Valerie, have always provided. My sisters and brothers-in-law, Adrienne and Mike, Elizabeth and Frank, and Sarah have been most supportive of me over the past two years and will always be very close to me, along with my two-year-old niece Allison, who daily grows into a more awesome and delightful person.

This page intentionally left blank.

Table of Contents

List of Tables

List of Figures

1 Introduction

1.1 A New Supply Chain Reality: Project Background

On March 11, 2011, the Wall Street Journal reported the following:

> Amgen Inc. (AMGN) is buying a ... manufacturing facility from Pfizer Inc. (PFE) for an undisclosed amount.
>
> The deal for the plant ... is expected to close in the second quarter. Pfizer had disclosed its plans to exit the site last May in a restructuring of its global manufacturing operations...
>
> ... Amgen will use the site to "formulate and fill" its biologic drugs, which means getting the proper dose in a bottle or syringe along with packaging and labeling.
>
> It plans to eventually expand manufacturing at the location. The move allows the company to expand its formulating and filling capabilities beyond its [primary] plant, and will "ensure continuity of supply" of its products, the Amgen spokeswoman said. (Gryta 2011)

The same day, Amgen's stock closed at $53.53, up 3.22% for the day, well above the same day close for the DJIA and Nasdaq (0.56% and 0.97%) respectively. Ranking days by Amgen's market-adjusted daily return reveals that this announcement is one of the six most impactful events in the past two years, alongside the announcement of the FDA's announcement of effective mid-trial results for and ultimate approval of denosumab, Amgen's ninth and most recent major product. This market response suggests that Amgen's decision is both significant in nature and well received by investors and Wall Street analysts.

On the day following the announcement of the new site acquisition, a second newspaper covered the story in further depth, reporting:

> "As we expand internationally, the [new] site will help us deliver a growing supply of Amgen medicines for patients worldwide," said Madhu Balachandran, senior vice-president, Amgen Manufacturing.(Coyle 2011)

Together, these stories point toward two fundamental operational challenges that Amgen seeks to address through the acquisition of the RMS:

1) an increasing complexity of production-distribution functions due to international expansion and resulting variety of product configurations (formulations, presentations and packages), and
2) the need to design a supply chain and production process robust enough to ensure continuity of supply, even in the face of "Black Swan" events, such as the recent earthquakes in Haiti and Japan.

The additional formulation and fill facility is geographically closer to new European markets (potentially addressing the first challenge) and quite distant from the current primary formulation and fill operations at Site 1A (potentially addressing the second challenge).

At the same time, the integration of this site into Amgen's production network presents its own challenges. Most notably, whereas Amgen once formulated and filled virtually all drug product ("DP") at Site 1A, the company must now decide what products to formulate and fill in what quantity at each site. Different manufacturing and distribution constraints (e.g. facility steel capacity) as well as costs (e.g. variable labor, transportation) at sites and between sites suggest that there is a significant financial benefit to optimizing production-distribution planning. Although Amgen only has nine major product families, it has over 75 different formulations and presentations (e.g. vial or pre-filled syringe), and hundreds of UPC's due to the need to package in different languages or test for different regulatory bodies.

This thesis develops a methodology to address how Amgen efficiently integrates the RMS into global operations as well as a tool to apply this methodology. The following sections describe the development of a Mixed Integer Linear Program ("MILP") that models Amgen's production-distribution network. We then apply this model to optimize production-distribution decisions by solving for the lowest network cost, subject to implied constraints and under various scenarios and/or assumptions. The concluding sections of this thesis discuss the strategic implications of the results of this model, as well as the limitations of this analytical approach.

1.2 Thesis Structure

The intended audience of this thesis has some familiarity with supply chain design and linear optimization, but little or no prior exposure to biotechnology. Thus, **Chapter 2** includes a general background on biotechnology and the biopharmaceutical industry, an introduction to Amgen, and a high-level view of their production-distribution network so as to inform the later sections.

The literature review presented in **Chapter 3** covers three distinct subsets of relevant literature. The first is a brief overview of prior relevant theses written by Leaders for Global Operations ("LGO") fellows, in the three years that Amgen has been a partner company of the LGO program. The purpose of this section is to present the context of other operations challenges on which Amgen has recently worked as well as point toward the operational maturing that Amgen has undergone in recent years. The second portion covers general issues in production-distribution system design. This section also outlines findings from some of the most salient prior reviews of literature in this field. The third and final section looks at prior theoretical papers and case studies in which a MILP was developed to solve a production-distribution optimization problem and compares these to the approach of this thesis.

Following the literature review, **Chapter 4** outlines the problem statement and methodology of this study. A detailed MILP is presented and specific aspects are discussed in detail. This section also covers the data sources that were used to populate the model, as well as a detailed description of data-preprocessing steps and assumptions.

Chapter 5 analyzes the results of the model, discussing how different sets of assumptions led to different outcomes and distills key recommendations to management from the most salient findings.

Chapter 6 concludes by reviewing the findings and recommendations and recommendations of this thesis. In addition, this section covers the issues of next steps and implementation, future work that Amgen can pursue in this field, and the limitations of the analytical approach employed.

2 Background

2.1 Biopharmaceutical Industry

Biotechnology is the branch of molecular biology that studies the use of microorganisms to perform specific industrial processes (Miller 2006). Beginning in the 1970s in Northern California, biotechnology has since grown into a global industry comprised of several sectors including healthcare, agriculture, and biodefense. Typical biotechnology processes work by inserting recombinant DNA, or DNA that has been modified through genetic engineering, into host cells. Using this information, host cells will then create recombinant proteins, the product of the biotechnology process (Amgen 2009).

The biopharmaceuticals industry is the branch of biotechnology that specializes in developing human therapeutics. The three primary functions of the biopharmaceutical industry are drug discovery, drug development and manufacturing. Drug discovery involves identification and validation of *targets*, or molecules that play important roles in a current unmet medical need, as well as screening processes to better understand the associated biomolecular pathway and ultimately design of a drug that will beneficially interact with the molecular target (Amgen 2009).

Drug development begins with preclinical studies in lab animals, followed by three phases of clinical trials that are closely monitored by either the Food and Drug Administration, or FDA (in the United States) or European Medicines Agency, or EMEA (in Europe). The three phases require the applicant company to evaluate the drug to determine, in sequence, safety, efficacy and effectiveness. While most investigational drugs fail in phase 2 trials, phase 3 trials are the most expensive and time-consuming, often requiring over two years to complete. During phase 3 an applicant company must show that the drug is more effective than current drugs on the market and is safe over a long period of time. Upon successful completion of phase 3 trials, a company completes a Biologic License Application with the relevant regulatory agency, after which time it can market the drug to patients (Amgen 2009).

The biopharmaceutical production process is described in detail in Section 2.3 below.

2.2 Amgen Inc.

Amgen, originally called American Molecular Genetics, was founded in 1980 as one of the first biotechnology companies and has since grown into a Fortune 500 company and one of the largest in biotech.

Amgen is a company of large impact through few products. Two of Amgen's early products, Epogen® and Neupogen® became the first biopharmaceuticals to gross over $1B in annual revenues, known as *blockbuster* drugs within the industry. Amgen continues to produce Epogen® as well as Aranesp®, both erythropoietic-stimulating agent ("ESA") used to stimulate the production of red blood cells and treat anemia. Neulasta® and Neupogen® both stimulate the production of specific white blood cells, frequently a critical post-chemotherapy treatment, and together account for over $4.5B of Amgen's annual sales. Amgen acquired the rights to market and produce Enbrel®, a leading anti-inflammatory drug used to treat rheumatoid arthritis, when they purchased Immunex in 2002 (Amgen 2009). Together the above drugs make up over 90% of Amgen's annual revenues as shown in Table 1 Table 1below.

	2009
Aranesp®	$ 2,652
EPOGEN®	2,569
Neulasta®/NEUPOGEN®	4,643
ENBREL	3,493
Sensipar®	651
Other	343
Total product sales	$14,351
Total U.S.	$11,135
Total International	3,216
Total product sales	$14,351

Table 1. Amgen 2009 Revenues by Product (Amgen 2009)

Other products include Sensipar®, used to treat secondary hyperparathyroidism in patients on dialysis, Vectibix®, a specific cancer treatment, and Nplate®, a platelet producer, and two new

medications based on the denosumab monoclonal antibody, Prolia® for postmenopausal osteoporosis and XGEVA® for skeletal-related events from solid tumors (Amgen 2009).

Amgen primarily manufactures its products in the United States and a nearby territory, but it also has a major European packaging facility as well as a manufacturing partnership with Kirin Holdings in Japan. The market for drugs, however is truly global: Amgen sells its drugs in 38 countries outside the United States, including Canada, Japan, Brazil, India, Hong Kong, Australia, New Zealand, the U.A.E., and almost all of Europe (Amgen 2009, 2011).

2.3 Biotechnology Production-Distribution Process Overview

Before developing a detailed mathematical model of Amgen's production and distribution processes, it is useful to present a basic overview of the processes.

The *first phase* of biotechnology drug production is bulk manufacturing. The first stage of this process, *scale up*, begin with the cracking of a vial containing a small number of dormant cells genetically engineered to create a specific protein that will eventually be formulated into drug product. *Scale up* begins with activation of the dormant cells in a small and progressively larger beaker. From that point throughout the entire bulk manufacturing process, the concentrations of glucose, lactic acid and other process by-products are monitored to maintain optimal cell replication and durability.

After 10-12 days of *scale up*, cells spend approximately 5-7 days in a *wave bioreactor*, which is a rocking mechanism that contains a large (up to 1000L) low density polyethylene/ethylene vinyl acetate (LDPE/EVA) copolymer bag that is pre-sterilized, irradiated and designed for single use. The benefits of wave bioreactors include their ability to scale from relatively low volumes to much larger volumes and the fact that they induce agitation and oxygen transfer by rocking the LDPE/EVA bag rather than by more invasive means such as mechanical mixing or gas sparging.

After the *wave bioreactor*, the mixture is transferred to a series of three to four stainless steel bioreactors for the large-scale process. The sizes of these bioreactors are largely dependent on the facility (e.g. the largest in a commercial manufacturing facility may be 15k L, compared to 2k L for a clinical manufacturing facility). In a typical three bioreactor setup, the mixture may spend 3 days in the first two bioreactors (60L and 300L in Amgen's clinical facility), followed by 11 days in the final 2k L bioreactor. In a commercial setting, this size may be the second to last step, in which case it would spend 3-4 days there following by 11-12 days in the largest bioreactor.

Altogether, the above steps are referred to as *upstream manufacturing* and comprise 32-40 days. The remaining steps, known as *downstream manufacturing* are performed after the concentration of cells and protein have reached their optimal level. These steps collectively take approximately one week and include *centrifuge*, *purification*, *viral inactivation*, multiple *chromatography* steps, *viral filtration*, *ultra-filtration/di-filtration* ("UFDF"), and *final filtration*. The output of this process is typically carboys or cryo-vessels of bulk *drug substance* ("DS") or *drug substance intermediate* ("DSI").

The *second phase* of biotechnology drug production is known as formulation and fill. This process, which is sometime but need not be collocated with bulk manufacturing, the DS is formulated to the FDA-approved concentrations (typically through dilution with a non-reactive, benign media), and then dispensed by a sterile needle-filling machine into a final container. The final container, or *presentation*, depends on the market need, but it is typically one of three: a vial, a lyophilized vial, or a pre-filled syringe ("PFS"). Lyophilization is the process by which a drug solution is freeze dried so that only the protein remains in power form. The benefit of this process is that it typically results in a longer shelf-life for the end product. However, it also requires more steps for the administrator of the drug, and can sometimes lead to a more pronounced stinging feeling when the drug is administered. Once filled, the drug is referred two as *drug product* ("DP"). Typically, inspection of the DP follows immediately, at which point the vials or syringes are referred to as *inspected drug product* ("IDP").

The *third phase* of the production process is packaging. During this phase the IDP is packaged for the end user. Typically multiple packaging configurations exist (e.g. kit or carton, top-load or side-load, one-pack or five-pack). This combined with the multiplicity of packaging and insert languages in international markets causes this step to be Amgen's key product differentiation step. For that reason, this step is often postponed for international markets.

The *final phase* of following the three production phases described above is distribution to customers. Customers are often large scale health systems, hospital systems, pharmacies or medical services providers. Depending on locations and distances, products are shipped via cargo ship, air freighter or truck. Figure 1 shows an overview of the production-distribution process described here.

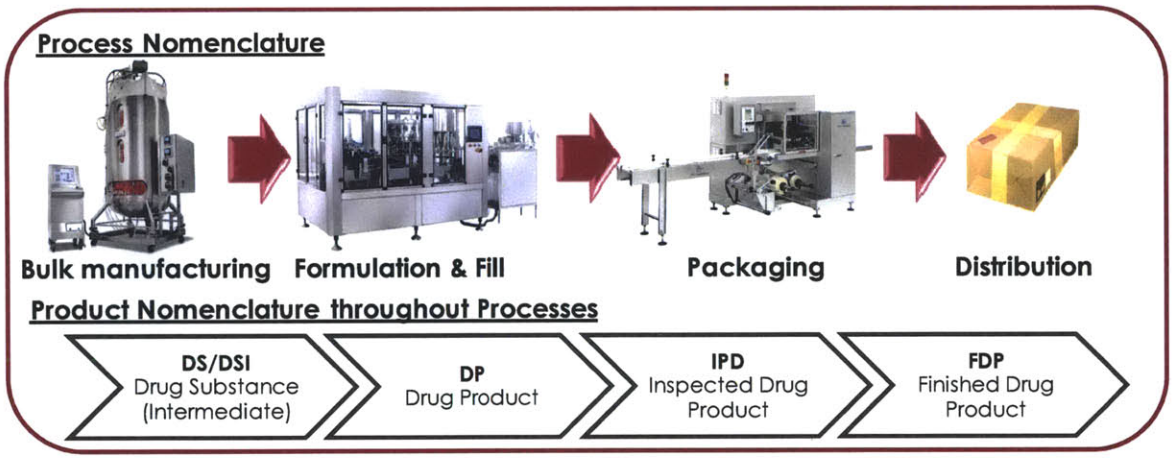

Figure 1. Biotechnology Production-Distribution Process Overview

From a logistics perspective, where these processes occur is almost as important as how they occur. The bulk manufacturing phase actually occurs in a variety of places. Possibly partly due to the fact that Amgen grew its product portfolio and manufacturing footprint through acquisition, the bulk manufacturing process is the most geographically diverse. Although Amgen's primary facility manufactures several drugs such as Aranesp, Neupogen, Neulasta, other drugs are bulk manufactured in places such as West Greenwich, RI (Enbrel), Fremont, CA (Vectibix), and Longmont, CO (Epogen, Nplate and Denosumab) (Amgen 2009).

The formulation and fill step, by contrast is much more highly concentrated. With the exception of a very small quantity of product, almost all of Amgen's DS and DSI is formulated and filled at Site 1A. As mentioned in the Wall Street Journal excerpt above, a desire to overcome this geographic concentration is at least part of the rationale for the acquisition of the RMS.

The packaging step is also concentrated, but by end market rather than global production. Site 1A handles almost all of the packaging for the US market (referred to as the North American Commercial Organization or "NACO"), and the European packaging site ("Site 2") handles most of the packaging for the European and other international markets (collectively referred to as the International Commercial Organization or "ICO").

For the NACO markets, distribution is managed by Amgen's primary U.S.-based distribution center. For ICO markets, Site 2 handles distribution as well. Figure 2 below gives a rough geographic picture of where drug product is bulk manufactured, formulated, filled, packaged and distributed in Amgen's current production-distribution system. A full profile of Amgen's geographic locations and processes at these locations is provided in Appendix E.

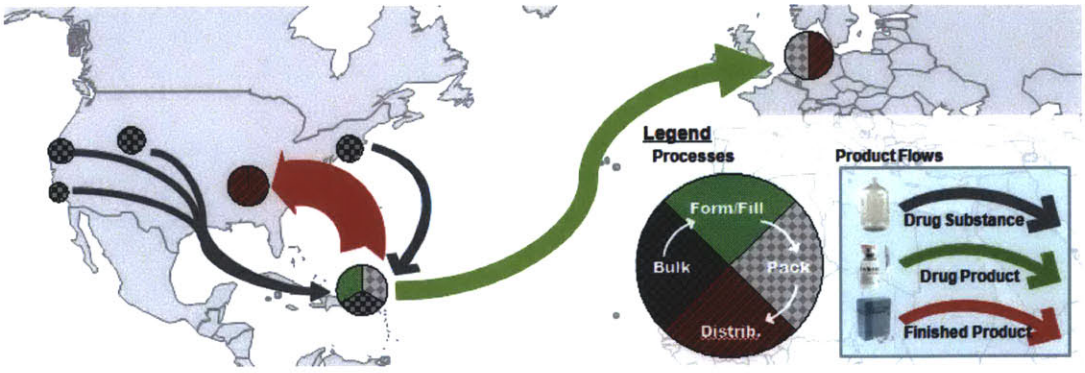

Figure 2. Production Capabilities and Product Flows

Looking at the above Figure, the operational planning challenge that Amgen will face upon expansion into a new formulation and fill facility is even more salient: as Site 1A currently fulfills this process for practically all of global demand, the formulation and fill scheduling can be optimized at the

facility level. Once a second plant is available, tradeoffs such as tax implications and transportation costs will need to be considered as they could have a significant impact on the suggested product allocation.

3 Literature Review

This section covers three distinct subsets of relevant literature. The first is a brief overview of relevant prior theses written by Leaders for Global Operations ("LGO") fellows. The second portion covers general issues in production-distribution system design as well as several prior reviews of this subject matter. The third and final section looks at prior theoretical papers and case studies in which a MILP was developed to solve a production-distribution optimization problem.

3.1 Prior LGO Theses

Amgen began its partnership with the LGO program in 2008, and in the three years since that time eleven theses have been completed. These theses can be roughly classified into three sub-groups: production process improvement studies, new production process business cases, and broad-reaching strategic managerial analyses.

Production process improvement studies were identified by the discussion of an existing process at Amgen, as well as the goal of improving outcomes through continuous improvement or Lean transformation. These theses include a high-level overview of the development of continuous improvement methodologies within Amgen's Operations Improvement group (Villa 2008), an analysis of the Amgen Process Excellence ("APEX") initiative (Coffey 2008), and a study of the impact that Lean and Six Sigma tools had on the cycle time of the buffer solution preparation process at Amgen Freemont ("AFR") (Jay 2009).

Theses classified as new production process analyses or business cases either introduced a new process or analyzed the impact a novel component would have on an existing process. New process studies included an evaluation of drying technologies rather than cryopreservation for DS storage and shipment (Vaudant 2008) and a case study on the implications of temporary markings on nude vials (Hardy 2010). One thesis looked at the changes to manufacturing processes due to a novel component,

specifically the impact of novel filtration applications for the removal of protein aggregates from drug solution (Hunnicutt 2008).

The remaining prior Amgen theses were classified as broad-reaching managerial analyses and are most similar in context to this analysis. These theses are characterized by the analysis of an analytical framework or decision tool that goes beyond the facility or production line unit of analysis. These studies included a strategic sourcing framework for bulk manufacturing at Rhode Island (Pasenek 2008), an analysis of the impact of Quality by Design principles on Amgen's commercialization process (Matthew 2009), and a case study how a greater cost focus affects the delivery of capital projects (Kristinsdóttir 2008). Two recent theses in this group developed a recommendation for Amgen's future approach to sourcing PFS components (Lee 2010), and an analytical framework to optimize Amgen's truck distribution system and distribution center location selection (Sekar 2010).

Two general comments can be made about the prior work by LGO fellows at Amgen. First, the focus of the analytical work tended to be more toward incremental process improvement rather than high-level strategic change. This traditional preference for process improvement work can be seen in Figure 3 below, a word cloud that represents frequency of occurrence of non-trivial words in all prior LGO Amgen theses. As can be seen in the figure, concepts related to manufacturing and process improvement are most salient, whereas issues of supply and distribution occur with a lesser frequency and topics such as simulation, optimization, and linear or mixed integer programming are not represented in prior LGO research at Amgen.

Figure 3. Word Cloud - Frequency of Terms in Prior LGO Theses on Amgen[1]

A second finding from the LGO literature review is that, despite the traditional bias toward process improvement work, the nature of work being performed at Amgen seems to be moving from realm of production process toward a greater focus on strategic, company-wide issues. Figure 4 shows how process improvement studies have diminished over the past few years, while theses with a more strategy focus have grown in proportion. It is difficult to say whether this trend reflects the preferences of companies or LGO fellows, but in either case, the outcome is apparent.

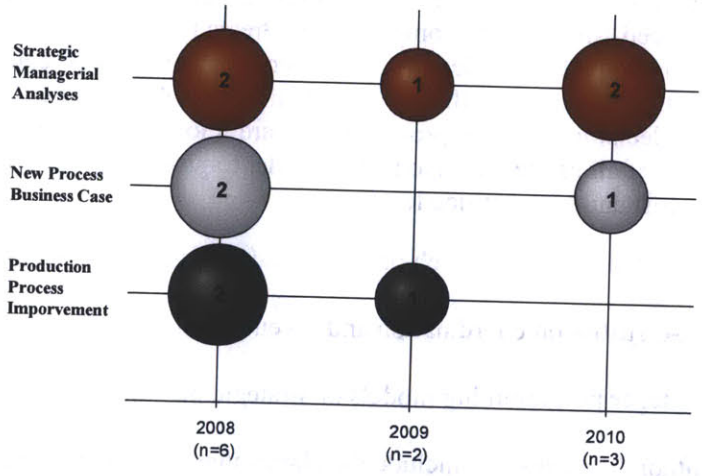

Figure 4. Number of LGO Theses by Author's Classification & Year

[1] Source: www.wordle.net. Note: The words "thesis," "Rhode," and "Island" were removed, along with commonly occurring English articles, conjunctions and pronouns.

3.2 Production-Distribution System Design and Prior Reviews

This sub-section briefly reviews the literature related to production-distribution system design per se as well as prior reviews of literature on this topic.

Shi and Gregory aim to classify different configurations of international manufacturing networks (1998). The authors suggest that international manufacturing network systems have all of the complexity of factory-based manufacturing systems (e.g. line capacity, technology, workforce and quality concerns) as well as network issues (e.g. geographic dispersion, horizontal and vertical coordination and dynamic capability building). In addressing these challenges, the authors claim that some organizations fail to develop the capabilities of network learning (e.g. wider internal and external comparison, best practices exchange and benchmarking) and thus become multi-domestic manufacturing rather than global coordinated manufacturing organizations (Shi and Gregory 1998).

Thomas and Griffin (1996) come to a similar conclusion, stating that:

> In the past, organizations have focused their efforts on making effective decisions within a facility. In this case, the various functions of an organization, including assembly, storage, and distribution are generally decoupled into their functional and geographic components through buffers of large inventories. In this way, the complexity of the decisions is reduced since each component is treated independently of the others. Ignoring these component dependencies, however, can have costly consequences. This becomes increasingly apparent with market globalization. As a result, firms are moving from decoupled decision making processes toward more coordinated and integrated design and control of all of their components in order to provide goods and services to the customer at low cost and high service levels.

Thomas and Griffin proceed to review research on three modes of global management (buyer-vendor coordination, production-distribution coordination and inventory-distribution coordination) and propose the use of either mixed integer programming models or strategic planning models to effectively manage these processes. The authors' conclusions include the claims that "long supply chains inhibit a firm's ability to respond quickly to consumer requirements," that "knowledge of all value-added activities in the supply chain is critical to coordinated modeling," and that "the single largest component of logistics cost is transportation cost, often comprising over half of total logistics cost" (Thomas and Griffin 1996).

Although the first two are helpful to keep in mind in the case of biopharmaceutical production-distribution processes, the third claim does not necessarily hold in this industry.

Diving deeper into the concept of transportation cost, Cooper presents the concept of value densities (the value of product in relation to its weight and volume) and competition. His paper gives examples of how low value density products (e.g. cement) are typical served by local catchment areas because transportation is a large component to price. Products with high value densities (e.g. precious stones or pharmaceuticals) have a much larger "logistics reach," but this reach can also be limited in highly competitive markets (Cooper 1993).

In addition to the above studies, which conceptually frame the challenge Amgen faces as it expands internationally, several other authors have provided exceptionally helpful reviews of the literature on international supply chain planning. Bhatnagar, Chandra et al. (1993) produced one of the earliest of these reviews, in which they classified coordination research into the same three categories as Thomas and Griffin. They laid the groundwork for production-distribution research that was to following, stating that:

> the multi-plant coordination problem seeks to link together the production plans of several manufacturing plants which are part of a vertically integrated firm, i.e., output from one plant becomes an input into another plant. The objective of such coordination is to achieve near optimal results on performance measures like total cost, manufacturing lead time etc., for the entire organisation. Coordination efforts must model the impact that production planning at one plant has on production planning at another plant. Such models must also take into consideration uncertainties associated with both the demand and the production processes (Bhatnagar, Chandra et al. 1993).

The authors then proceeded to identify three key challenges/objectives that continue to be important today: nervousness (e.g. variability of demands on a plant due to internal issues such as scheduling adjustments or forecast updates), lot sizing and safety stock.

Vidal and Goetschalckx (1997) go a step further than prior literature reviews, by also providing a very helpful taxonomy of relevant optimization models including Geoffrion, Graves, et al. (1973), Brown,

Graves, et al. (1987), Cohen and Lee (1988), Cohen and Moon (1991), and Arntzen et al. (1995). In summary, the authors conclude that:

> The main drawback of these models is the fact that most uncertainties are not considered in the formulations. In addition, there does not exist a formal and consistent way to represent BOM constraints. Moreover, some international factors, such as exchange rates, taxes, and duties are not fully described by the existing models ... We think that future research should concentrate on the development of an overall global logistics framework, supported by multiple inter-related models capable of representing qualitative factors and uncertainties. This framework must include MIP models as a fundamental part, and interact with management in a coordinated way to solve specific problems. However, such a framework will remain a decision support tool, not a replacement of the decision-maker function (Vidal and Goetschalckx 1997).

Beamon analyzed multiple supply chain models and performance measures developed in the literature (1998). She summarized various objectives models were designed to optimize (cost, customer, responsiveness, cost and customer responsiveness, cost and activity time) as well as the direction of this optimization (e.g. minimize cost or maximize profit, minimize stockout probability or maximize available system capacity). Ultimately, Beamon suggests that future research focus on the following four areas: "(1) evaluation and development of supply chain performance measures, (2) development of models and procedures to relate decision variables to the performance measures, (3) consideration of issues affecting supply chain modeling, and (4) classification of supply chain systems to allow development of rules-of-thumb or general techniques to aid in the design and analysis of manufacturing supply chains" (1998).

In a more recent literature review on the same subject, Peidro, Mula et al. (2009) outline four types of supply chaining models (analytical, artificial intelligence, simulation and hybrid) under one to three types of uncertainty (demand, process, and supply) to address three types of problems (strategic, tactical, and operational). They find that most models address only one type of uncertainty (59.2%) whereas less than 10% address all three simultaneously. They suggest that artificial intelligence models are becoming more dominant as supply chain modeling becomes increasingly complex. Finally, the authors provide several suggestions for future work, including the development of more models that integrate multiple sources of uncertainty and further empirical studies to compare the applicability of various modeling approaches.

3.3 MILP Formulations and Relevant Case Studies

Tsiakis and Papageorgiou (2008) employ a MILP to solve for optimal production allocation and distribution in a generic three-echelon supply chain network comprised of production plants, distribution centers and customer demand zones. The authors' model is the only reviewed that explicitly incorporates tax and duty costs, which is specified for each product, plant and customer zone combination. Additionally, this paper includes the concept of time utilization for plant maintenance as well as changeovers. Their formulation allows for multiple campaigns for each product-production plant pair, but a weakness is that this quantity is set as a parameter, thus constraining the possible set of solutions considered by the MILP. Furthermore, although the authors consider unit production costs that vary by product-plant pairs, the specified daily production rate varies by plant only, thus assuming all products are produced at the same rate.

Thanh, Bostel et al. (2008) develop a MILP to optimize production-distribution in a four-echelon supply chain (suppliers, plants, warehouses, customers). Allowing for multiple products, this model is novel in that it includes fixed costs for supplier selection, facility opening/closing and election of specific operating capacity expansion options. Addressing one of the weaknesses in Tsiakis and Papageorgiou (2008), the authors allow for different per-unit workloads for each product-plant pair. On the other hand, they do not account for changeover costs or the issue of production campaigning. Thus, this model either assumes that these factors do not consume capacity, or that they do so but on a fixed per-unit basis (incorporating it into the per-unit production workload factor).

Gebennini, Gamberini et al. (2009) also develop an integrated production-distribution model to specify both facility location and product allocation under uncertainty. Using a three-echelon supply chain (comprised of one central production and distribution center ("CDC"), multiple regional distribution centers ("RDCs"), and multiple points of customer aggregation), the authors aim to solve long-term strategic planning, short-term tactical planning, and day-to-day operational planning in an integrated MILP. According to the authors:

this problem configuration aims to answer three fundamental and interrelated questions: *where* is the best place to locate the available facilities, *what* size is the best capacity to assign to the generic logistic facility, and *when* in a specific location demand occurs requiring a certain amount of production capacity, i.e. the periods of time this capacity is required (Gebennini, Gamberini et al. 2009).

The key contribution of this paper is the authors' approach to accounting for uncertainty in demand: they include a factor for safety stock ("SS"), or the minimum amount of inventory that a company seeks to have on hand to guarantee a certain service level in the face of uncertain demand. As this term grows in proportion to the square of production, the authors employ a ad-hoc solving procedure in order to keep a linear cost minimization objective function. This approach is illustrated below:

1. The initial SS cost term is non-linear:

[1]

$$\sqrt{\sum_{L}(c_k)^2 s^2 \sigma_{kl}^2 \vartheta_{kl}}$$

where: L = set of demand locations; c_k = unit inventory cost/unit time in RDC k; s = safety factor to control consume service level; σ_{kl} = combined variance at RDC k service the point of demand l ; ϑ_{kl} = binary decision variable, assuming value of 1 if RDC k supplies the point of demand l in any unit time t, 0 otherwise (Gebennini, Gamberini et al. 2009).

2. However the authors note that the values of binary variable θ_{kl} that minimize the below linear equation will be the same as the corresponding ϑ_{kl} terms that minimize the above non-linear SS cost at the each RDC:

[2]

$$\sum_{L}(c_k)^2 s^2 \sigma_{kl}^2 \theta_{kl}$$

(Gebennini, Gamberini et al. 2009)

Because c_k, s, and σ_{kl} are all constants in Equation [2], this equation is linear with respect to θ_{kl}, which, like ϑ_{kl}, is a binary decision variable.

3. Simply substituting this term into the objective function will cause it to underestimate the weights of the other terms, thus compromising the minimization. To correct this effect, the authors next divide the term by SS_k, which represents the lower bound of the optimal amount of SS carried at the RDC k. Initially, or for the first iteration i, the authors set $SS_k^{(i-1)} = SS_k^{(0)} = s * \min_{l \epsilon L} \sigma_{kl}$. They then perform a linear optimization, at the end of which they set:

$$SS_k^{(i)} = \begin{cases} s\sqrt{\sum_L (c_k)^2 \sigma_{kl}^2 \vartheta_{kl}^{*(i)}} & if\ RDC\ k\ was\ utilized\ in\ iteration\ i \\ 1 & if RDC\ k\ was\ not\ utilized\ in\ iteration\ i \end{cases}$$

(Gebennini, Gamberini et al. 2009)

4. These iterations are repeated until none of the $SS_k^{(i)}$ terms are updated, at which point a good linear approximation of is estimated. The authors then go on to solve the original nonlinear model, but as this is outside the scope of this thesis, that analysis will not be reviewed in detail.

Gebennini, Gamberini et al. (2009) also apply their model to the distribution network of an Italian electronics company. In this real case study, the authors find that optimization can yield a 10% saving on global logistics costs. This savings is the result of an increase in costs on the RDC-customer transportation leg (34%) offset by significant reductions in CDC-RDC logistic cost, RDC fixed cost, and SS inventory holding cost (respective savings of 48%, 44% and 19%) (Gebennini, Gamberini et al. 2009).

Corsano and Montagna (2011) further develop the capacity option concept in Thanh, Bostel et al. (2008) by integrating batch plant design decisions into a typical production-distribution allocation formulation. Considering a four-echelon supply chain (raw material sites, manufacturing plants, warehouses, and customer zones), the authors develop a MILP that seeks to minimize total cost define as equipment cost, operating cost and logistic cost. Equipment cost includes the cost of manufacturing lines and storage tanks that would enable duplication in or out of phase for a batch manufacturing process (modeled after the chemical industry). Operating costs include the raw material cost, warehouse operating cost and production cost and logistics costs include transfer of materials and goods between the four echelons. One weakness of Corsano and Montagna's approach is the fact that they assume plants

operate in single product campaign ("SPC") mode throughout the time horizon of analysis, an assumption that does not hold in Amgen's situation.

Corsano and Montagna proceed to solve for the optimal total cost in two manners: (1) simultaneously, as designed, and (2) sequentially, in which they first solve the production-distribution problem assuming plant capacities are not constraining and then perform a secondary optimization for the plant-level investments. Although the second method is likely a closer analogue for typical corporations that do not do extensive long-range capital planning, the salient point from this study is that it typically leads to slightly lower logistic costs (6.5-14% reduction depending on echelons) but significantly higher investment costs (50.5% increase), leading to a total network cost increase of 18.5% (Corsano and Montagna 2011).

Additional relevant studies were reviewed for comparison but are not examined in detail as the findings or approach to not uniquely inform this thesis. These sources include Cohen and Lee (1988), Cohen and Moon (1991), Hodder and Dincer (1986), Tsiakis, Shah et al. (2001), and Zhang, Huang et al. (2009). The key aspects of these models, as well as those in the above papers, are summarized below in Table 2.

The MILP described in this thesis aims to incorporate the best aspects of these above studies. As international shipments and tax issues are relevant to the biopharmaceutical industry, it will seek to incorporate the approach to duties on shipments outlined in Tsiakis and Papageorgiou (2008), taking this further to incorporate production-location-specific revenue and profits taxation scenarios. Similar to Gebennini, Gamberini et al. (2009), the proposed MILP formulation aims to capture the impact of demand uncertainty on network costs through the estimation of safety stock holding cost. Finally, this thesis will also leverage the concept of fixed capacity options proposed in Thanh, Bostel et al. (2008) and further developed in Corsano and Montagna (Corsano and Montagna 2011). Although Amgen is not

currently looking at specific investment decisions, capacity options will be considered from a human resources perspective, which is equally relevant in this industry.

			Model													
			Structure													
Authors	Year	Case Study	# of Echelons	Network Configuration*	Raw Mat. sites	Production plants	Central depots	Regional depots	Customers	Raw Materials	Products	Approach	Multi-period	Prod. lead time	Safety stock	
Author's approach	2011	Amgen, Inc.	3	RM-PF-RDC	Yes	Yes		Yes		Multiple	Mutiple	MILP	Yes		Yes	
Cohen and Lee	1988	Example only	3	RM-PF-RDC	Yes	Yes		Yes		Multiple	Mutiple	Multiple Heuristic				
Cohen and Moon	1991	Example only	3	RM-PF-D	Yes	Yes			Yes	Multiple	Mutiple	MILP				
Corsano and Montagna	2009	Example only	4	RM-PF-RDC-D	Yes	Yes		Yes	Yes	Mutiple	Mutiple	MILP				
Gebennini, Gamberini et al.	2011	Italian electronics company	4	PF-CDC-RDC-D		Yes	Yes	Yes	Yes		Single	MILP, MINLP	Yes	Yes	Yes	
Hodder and Dincer	1986	Example only	2	PF-D		Yes			Yes		Single	LP				
Shah and Pantelides	2001	Example only	4	PF-CDC-RDC-D		Yes	Yes	Yes	Yes		Mutiple	MILP				
Thanh et al.	2008	Example only	4	RM-PF-RDC-D	Yes	Yes		Yes	Yes		Mutiple	MILP	Yes	Yes		
Tsiakis and Papageorgiou	2008	Example only	3	PF-RDC-C		Yes		Yes	Yes		Mutiple	MILP				
Zhang and Huang	2009	Hypothet. shoe mfg	3	RM-PF-D	Yes	Yes			Yes			MILP				

			Model (cont'd)								Case Study / Example							
			Costs Included								*Inclusion and Size of Inputs*							
Authors	Year	Case Study	Invest-ment	Var. Prod. (units)	Var. Prod. (lots)	Prod. Facility	Duty/ Taxes	Transpor-tation	Warehouse /DC Facility	Inventory Holding	Stockout Penalty	Raw Mat.	Pro-ducts	Raw Mat. Sites	Prod. Plants	Central Depots	Reg. Depots	Demand Zones	Time Periods
Author's approach	2011	Amgen, Inc.	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		6	65	3	2		2		5
Cohen and Lee	1988	Example only		Yes	Yes	Yes		Yes	Yes	Yes		3	2		1		3		
Cohen and Moon	1991	Example only		Yes	Yes	Yes		Yes					3		4			10	
Corsano and Montagna	2009	Example only	Yes	Yes		Yes		Yes	Yes	Yes		3	4	6	5		5	45	
Gebennini, Gamberini et al.	2011	Italian electronics company		Yes		Yes		Yes	Yes	Yes	Yes		1		Multiple	1	5	>1100	30
Hodder and Dincer	1986	Example only		Yes			Yes	Yes					1		7			10	
Shah and Pantelides	2001	Example only		Yes		Yes	Yes	Yes	Yes				14		3	3	3	18	
Thanh et al.	2008	Example only	Yes	Yes		Yes		Yes	Yes	Yes			5		9		9	160	5
Tsiakis and Papageorgiou	2008	Example only		Yes		Yes	Yes	Yes	Yes	Yes			6		6		6	8	
Zhang and Huang	2009	Hypothet. shoe mfg		Yes	Yes	Yes	Yes			Yes			1	2	**			**	

* RM=Raw Material Site; PF=Produciton Facility; CDC=Central Distribution Center; RDC=Regional Distribution Center; D=Demand Zone, Point or Customer

**Information not available in source

Table 2. Production-Distribution Models Reviewed in This Work

4 Problem Statement and Analytical Approach

4.1 Problem Statement

The purpose of this thesis is to provide an analytical framework for making production decisions for the formulation and fill manufacturing step (at a strategic high level if not tactical level). Specifically, the model is designed to analyze how these decisions would change over the 2013-2017 time frame, during which it is anticipated that i) Site 1B will come online as a formulation and fill site and ii) the additional site referred to as RMS will be brought online. Because Amgen's production-distribution system prior to this acquisition takes the form of a directed arborescent network,[2] each product could only take one path through the four manufacturing/distribution steps to a customer. The addition of RMS, however, causes their supply chain to take the form of a directed nonarborescent network, where the set of nodes enable multiple production scenarios and thus presents an opportunity for optimization (see Figure 5 below).

Fundamentally, developing a form/fill production allocation plan or strategy is about answering a single question: *how many lots of product of a given size should we produce in each facility in each year?* However, this question becomes more complicated when one considers that multiple lot sizes are available for each product. Additionally, to analyze capacity simultaneously, the situation becomes even more complex, because this adds the additional question: *how many hours of capacity should be established at each site in each year?* Clearly the answer to each question is dependent on the other. Aside from this dependency, the problem facing Amgen is even more complex due to the number and variety of unknowns: the number of potential outcomes is a factor of the roughly 75 DP SKUs, each with

[2] *Arborescent* literally means *tree-like* and *directed* means that product can only flow in one direction (in this case from bulk sites to fill/finish sites and finally to distribution centers). Together these terms mean that, viewed in the direction of allowable product flow, nodes in each echelon following the first (bulk sites) can have exactly one upstream node and zero or more downstream nodes. The implication of an arborescent structure is that there is only one path to get any material to any node in the network. Each node in a *nonarborescent* network, by contrast, can have multiple upstream nodes, thus the number of ways product can get to each node becomes a factor of the number of nodes connected to it in each upstream echelon, resulting in a much more complex production allocation problem.

1-8 frequently used lot sizes matched against 2-3 sites, each with 2-4 potential shift structures (and associated costs and hours capacity).

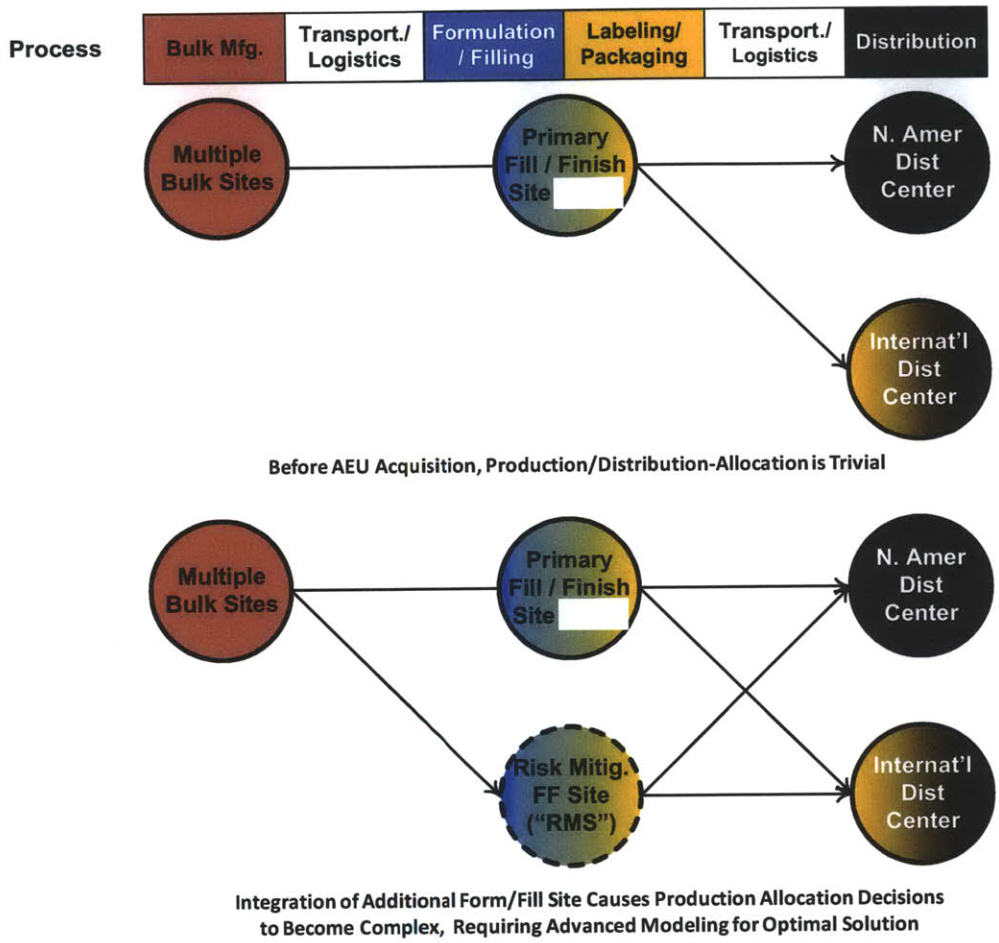

Figure 5. Network Representation of Supply Chain, Before and After New Facility Acquisition

All of these factors relating to product decisions or capacity decisions directly or indirectly have a cost associated with them. Staffing costs will increase once a given staffing level is insufficient to meet marginal demand requirements. Raw material, transportation lane or tax costs can be considered to be incurred with the flow of each marginal unit of product. The holding cost of cycle inventory would depend on the lot sizes produced for each product, and thus would not necessarily rise or fall with an increase in total demand, as production frequency, but not lot size, would necessarily have to increase to

meet increases in demand. The holding cost of safety stock, by contrast, is typically assumed to increase in proportion to the square root of production levels, although in this thesis we will see that this increases at a slightly faster rate.[3] Altogether, it is important to note that cost is directly or indirectly tied to each factor in this model, and as we are seeking to optimize the decision at hand, our goal will be to minimize the total of these costs.

[3] Safety stock is typical estimated as $Z\sigma\sqrt{L}$, where Z is the service factor, or the inverse of the standard normal cumulative distribution for the desired Type I service level (i.e. 2.33 for 99% Type I service level), and $\sigma\sqrt{L}$ is the standard deviation of unbiased forecast errors for lead time demand. As described in Section 4.3.4 and Appendix A below, the square root relationship does not hold here and can be better approximated by $L^{0.8}$.

4.2 Methodology

In order to address the challenge of simultaneously optimizing product flows, batch size selection and capacity levels as described above, a mixed integer linear program ("MILP") was developed. As is shown below, binary decision variables are necessary in some cases (e.g. facility active flag) and integer decision variables are desirable (e.g. in the case of deciding a number of batches to produce). Thus an MILP is preferable to a standard linear program (LP), although selecting the former limits some of the ways the model can be used to perform sensitivity analyses. Furthermore, every effort was maintained to keep this model linear in order to limit computational complexity.

As the aim of this thesis is to direct the formulation and fill production allocation decisions of DS→ DP/IDP, rather than the packaging allocation decisions of IDP → FDP, the production network in the MILP is modeled after the diagram in Figure 5 above. Thus, the packaging step will be considered integral in either the formulation/fill or the distribution process. Following from this, neither the relatively insignificant production costs nor any logistics costs associated with the packaging process are included in the MILP. This simplification is reasonable because packaging currently occurs at either Site 1A, which is the current sole formulation/fill plant, or Site 2, which is the primary distribution center for the international markets. Thus the only exception to this assumption would be product that is filled at the RMS and then sent to the United States for final distribution. This small amount of product could either be diverted through Site 1A/B for packaging or packed by a third party contractor at a minimal incremental cost, and thus our assumption holds.

In consideration of our goal of minimizing cost, the fact that production allocation decisions and capacity allocation decisions are dependent on one another, and the sheer number of factors under consideration, we must move beyond traditional analytical tools such as Excel in order to sufficiently optimize such a model. Given the size of this model, IBM ILOG CPLEX Solver was selected for this task.

4.3 Mixed Integer Program Formulation

4.3.1 Model Indices and Data Sets

I $(i \in I)$ set of products, specifically Inspected Drup Product (IDP) SKUs

J $(j \in J)$ set of formulation and fill facilities in network

L $(l \in L)$ set of distribution centers (DCs) at which points demand will be aggregated

E $(e \in E)$ parametrized set of batch size available for each product

S $(s \in S)$ set of shift structures available at each facility (e. g. 5day x 24hr x 1line ...)

N $(n \in N)$ set of indexed years in analysis (i. e. 1 ... 5 for years 2011 – 2015)

4.3.2 Decision Variables

x_{ijlen}

= lots of DP i, of size e that are to be formulated, filled and finished (FF'd)at facility j and then sent to distribution center l for packaging, in year n

ψ_{jsn} = boolean for wheter or not shift structure s is implemented at facility j in year n

f_b_{ijen} = boolean for whether or not lot size e is selected for product at facility j in year n

4.3.3 Optimization Objective Summary

The objective function is comprised of four key terms: (1) the linear variable costs of production, (2) the variable staffing costs to maintain facilities at a given level of production, (3) the annual variable holding cost of cycle inventory (raw materials, WIP and finished goods), and (4) the annual variable holding cost of safety stock. As this is a total cost function, the objective of the model is clearly to minimize it.

Linear variable costs are defined as the sum of two terms: (1) units produced multiplied by the variable costs of production and (2) number of lots multiplied by the incremental lot setup cost. Staffing costs were calculated outside the model for each staffing scenario (see Appendix B for a full discussion), and are included for all facility-staffing structure combinations that the model implements. Cycle inventory cost is assumed to be the incremental annual holding cost of one half of the sum of all lot sizes of unique products produced at a given site. This calculation follows the assumption that inventory is consumed in an approximately linear manner, so that over time the average amount of inventory of a given product that a site has on hand is one half of the production lot size of that product. As discussed above, the safety stock requirement for a given service level, and thus the holding cost of safety stock, is typically assumed to grow at a rate determined with the square root of demand. In the case of demand for Amgen's drug product or inspected drug product, however, the appropriate exponent of demand was empirically determined to be approximately 0.8. The calculation of this exponent is discussed further in Appendix A.

In developing this objective function and collecting data to populate it, we made every effort to collect only those costs that are variable, as only these should drive the outcome of the model and business decisions. For example, since warehouse requirements were unlikely to change for a marginal increase or decrease in cycle inventory or safety stock, we ignored the warehouse cost term in calculating total inventory holding costs.

4.3.4 Objective Function

Minimize

$$\sum_{ijlen}\left(\left(\left(f_{ije} * b_{ijl}\right) + \eta_{ij}\right) * x_{ijlen}\right) + \qquad \text{[\$, linear variable costs]}$$

$$\sum_{jsn}\left(\psi_{jsn} * \pi_{jsn}\right) + \qquad \text{[\$, staffing costs]}$$

$$\frac{(\tau_{ij} * WACC) * \sum_{ijen}(f\_b_{ijen} * f_{ije})}{2} + \qquad \text{[\$, cycle inventory holding costs[4]]}$$

$$c_{ij} \sum_{ijn} \sum_{el}\left(\left(f_{ije} * x_{ijlen}\right)^{0.8} * LT_{ijl}{}^{0.6}\right) \qquad \text{[\$, safety stock inventory holding costs][5]}$$

where f_{ije} = lot size in scenario e for product i at facility j [units/lot]

b_{ijl} = total linear costs per unit to ship to and FF IDP i at facility j, and then ship to DC l [\$/unit]

η_{ij} = incremental lot setup cost for product i at facility j [\$/lot]

π_{jsn} = annual incremental cost of implementing shift structure s at facility j in year n

τ_{ij} = replacement cost (incremental value) per unit of IDP i at facility j [\$/unit]

LT_{ijl} = production lead time for drug product i at facility j demanded by dist. ctr. l

c_{ij} = safety stock holding cost for product i at facilty j [\$/unit]

$$= \tau_{ij} * WACC * Z_{service\ level} * K$$

where

[4] In both cases of holding costs, warehousing costs are considered fixed (sunk) and ignored. Thus, holding costs only include the cost of capital invested in inventory.

[5] See Appendix A for explanation of 0.8 and 0.6 exponents.

$WACC =$ weighted average cost of capital or appropriate discount rate

$Z_{service\ level} =$ inverse of the standard normal cumulative distribution function for the desired service level [dimensionless]

[3]

$$K = \frac{\sigma_{forecast\ error\ of\ demand}}{(IDP-FDP\ lead\ time)^{0.6}(exp.demand\ over\ lead\ time)^{0.8}}$$

Using the best available data from the sources described in Section 4.4 below, we collected data to populated f_{ije}, b_{ijl}, η_{ij}, and τ_{ij}. In calculating η_{ij}, we assumed a 2kg loss of drug substance per fill batch (as is typical of this process), and multiplied this amount by the cost/gram of the drug substance.

Staffing costs are a considerable expense and represent a leading driver of model results under many scenarios. Each π_{jsn} value represents the cost of a feasible shift structure that provides for up to a certain number of production hours. Because this schedule depends on selectively staffing or not staffing different production lines, costs do not increase linearly but rather exhibit step-function changes that have important implications to the model outputs. See Appendix B and Appendix C for a thorough discussion of this approach.

Throughout the study, we assumed a 10% WACC and a 99% Type I service level, which results in a Z value of 2.33. Although we developed the model in a robust manner to accommodate various production lead times, we set LT_{ijl} equal to 1 month for all products, facilities and distribution centers, as corresponds to the typical lead times for these products. K in Equation [3] is dimensionless, and, as we show through an empirical analysis described in Appendix A, is approximately equal to 0.8, which is constant across all products.

4.3.5 Supply Chain Network Constraints

For convenience of terminology, let $X_{ijln} = \sum_e f_{ije} * x_{ijlen}$, or the total amount of production in units FDP produced.

4.3.5.1 *Demand constraint*

All demand for all products i at distribution centers l must be fulfilled in each year n, thus:

$$\sum_j X_{ijln} \geq D_{iln} \qquad \forall i, l, n$$

where D_{iln} = demand for product i in DC l in year n [units/year]

4.3.5.2 *Formulation/fill facility capacity constraint*

The amount of time consumed (both in changeovers and production runs) in facility j in year n, must be no greater than the time available per the chosen shift structure, thus:

$$\sum_{iel}\left((x_{ijlen} * \xi_{ij}) + \left(X_{ijln}/(60 * \zeta_{ij})\right)\right) \leq \sum_s(\phi_{jsn} * \psi_{jsn}) \qquad \forall j, n$$

where ξ_{ij} = lot setup time for product i at facility j [hours/setup]

ζ_{ij} = production line speed for product i at facility j [units/minute]

ϕ_{jsn} = hours available under shift structure s at facility j [avail hours/year]

Note that unlike the other capacity constrained production-allocations/distribution models discussed in Section 3.3, this model uses a capacity constraint that takes both lot size and number of lots into account when determining capacity consumption. Refer to Appendix B for a detailed discussion of how we calculated these factors, which we performed as a data pre-processing step before the MILP was run.

4.3.5.3 *Single shift structure per time period*

Each facility j can only be specified to have one shift structure s in each year n, thus:

$$\sum_s(\psi_{jsn}) \leq 1 \quad \forall j, n$$

4.3.5.4 *Single lot size selected per facility and time period constraint*

For the validity of the cycle stock inventory cost component to hold, as defined, each product i can have at most one selected batch size e in each facility j and year n, thus:

$$\sum_e f\_b_{ijen} \leq 1 \qquad \forall\, i,j,n$$

4.3.5.5 *Risk Mitigation Site maximum production constraint*

Per a hypothetical arrangement, RMS would be limited to produce no more than an assumed percentage of the total demand for any product family in any year. We formulated this constraint as follows:

[4]

$$\sum_{i\in R,l} x_{i,EU,len} \leq (allowed\ \%) * \sum_{i\in R,l} D_{iln} \qquad \forall\, R,n \quad \text{(ALTERNATIVE 1)}$$

where $R =$ set of product families, each containing a set of IDP SKU's i

Alternately, we could consider a similar constraint, whereby RMS is limited to a percentage of global aggregate production, rather than by each product family. In this case, Equation [4] would become:

$$\sum_{i,l} x_{i,EU,len} \leq (allowed\ \%) * \sum_{i,l} D_{iln} \qquad \forall\, n \qquad \text{(ALTERNATIVE 2)}$$

4.3.5.6 *Risk Mitigation Site minimum production constraint*

In actuality, per-unit costs (production, logistics, etc.) could typically be higher at either RMS, Site 1A, or Site 1B. If this were the case, we would hypothesize that an unconstrained optimization model might suggest filling/finishing all product at whichever site had the lower cost, as doing so would reduce fixed costs. Irrespective of this consideration, however, we assume that RMS should be able to ramp up to full capacity within 3 months of an adverse occurrence at the Site 1A/B. This translates to a minimum product flow constraint through RMS that will keep the facility sufficiently staffed to prepare for a fast ramp-up. In order to maintain this minimal amount of production at RMS, we determined that it should produce at least one batch of each product in each year. We formulated this constraint as follows:

$$\sum_{le} x_{i,RMS,len} \geq 1 \qquad \forall\, i,n$$

4.3.5.7 *Within selected lot size constraint*

This constraint exists for purposes of the MILP and prevents the program from specifying the production of any batches where that batch size has not been selected for the given facility and year.

$$\sum_l x_{ijlen} \leq M * f\_b_{ijen} \qquad \forall\, i,j,e,n$$

4.3.5.8 *Minimum production frequency constraint*

The concept of minimum production frequency ensures that Amgen will produce enough inspected drug product ("IDP") with sufficiently long shelf-lives to serve young markets that have an exceptionally high Remaining Shelf Life ("RSL") requirements on shipped finished drug product ("FDP"). We formulate this constraint as:

$$\sum_{jle} x_{ij,ICO,en} \leq \alpha_{il} \quad \forall\, i,n$$

where

[5]

$$\alpha_{il} = \text{min prod frequncy of product } i \text{ given regulatory constraints of}$$

$$\text{markets within ICO footprint } \left[\frac{\text{lots}}{\text{year}}\right] = \frac{shelf\ life_i}{(shelf\ life_i - \max RSL_{il})}$$

In Equation [5], $maxRSL_{il}$ is the most restrictive remaining shelf life requirement that exists amoung all of the end customers within the demand zone served by distribution center *l*.

4.4 Data Sources

There are two groups of people:

those who can extrapolate from incomplete information

- @ErikBryn (HT: @Delong)

This section provides a high level overview of the data sources and data preparation that was performed prior to running to model described above. More in depth discussion of specific items can be found in the Appendices referenced herein.

We acquired product-specific data from a variety of sources, including Amgen's *Cognos* database for unit demand forecasts. *Rapid Response* Bill of Material (BOM) data enabled us to match FDP SKUs to DP SKUs and thus aggregate demand at the DP level. *Rapid Response* was also the source of bulk cost per active gram (DS) and actual cost per unit DP which enabled us to estimate variable production costs (per an assumption plugged into the model).

We developed capacity options using data from a variety of sources, and the methods for this are described in detail in Appendix B. We used current facility audits for Site 1A as a baseline for available hours. From this, we increased or decreased time depending on different shift arrangements for a single crew per line type (vial or syringe), a single crew per line type plus a shared setup crew, or two crews and two setup crews. We based approximate facility staffing needs on existing plant headcounts at Site 1A and cost per headcount was provided by the finance group supporting operations. Together this information was sufficient to provide a set of options and costs for different levels of capacity. For the different formulation/fill facilities (Site 1B and RMS), we applied factors to both the headcount costs and line hours available (as each site will have one vile/one syringe line rather than two). These factors are explicitly defined assumptions that are incorporated into the data pre-processing steps before the model is run.

We derived production requirements by product from the recent capacity audit performed at Site 1A by members of the operations strategy group. The key elements of this data are available hours (after deducting for holidays, planned maintenance, etc), production run rates by product and changeover times by product (including line clear and sterilization steps). As this study was performed on the plant level, not the line level, we made the simplifying assumption that any available capacity can be utilized to produce any product. In reality, vial lines and syringe lines are entirely different, which would require this to be re-examined should such a model be used for plant-level scheduling optimization. In addition to the audit data, corporate planners for each product provided a list of validated batch ranges for their respective SKUs. These were indexed from 1-8 and incorporated into the model as index *e*. In the same manner as capacity, production requirements from Site 1A were multiplied be factor assumptions for Site 1B and RMS.

Finally, we collected transportation lane data from the transportation group. For each potential transport lane in the model, this data includes two components: freight cost and shipping container cost. The predominant shipping container used for long-distance travel is the P-002 bulk shipper. These are a considerable portion of the overall shipping cost for any lane and, although they are rated for multiple uses, are often discarded after one shipment. Thus, we assumed that P-002's are fully expensed with each shipment.

4.5 Model Implementation

4.5.1 Modification to Model for Linearity

As mentioned in Section 4.2 above, we utilized the IBM ILOG CPLEX Optimization Studio, based on the CPLEX algorithm, to program and run the above model. The CPLEX algorithm is an implementation of the simplex method in the C programming language, first developed by Robert E. Bixby and available for commercial purposes in 1988 (Wikipedia 2011). It is important to note that, although this algorithm is capable of solving integer, very large linear, and convex quadratic

programming problems, it is not capable of solving nonlinear or mixed integer nonlinear programming problems.

In order to use CPLEX to solve the mixed integer program formulated in Section 4.3 above, we made some modifications to make this a truly linear programming problem. Recall that the safety stock cost (one term in the objective function) is defined as:

[6]

$$c_{ij} \sum_{ijn} \sum_{el} \left(\left(f_{ije} * x_{ijlen} \right)^{0.8} * LT_{ijl}{}^{0.6} \right)$$

Because x_{ijlen} is a decision variable, representing the number of lots of product i of size e that are produced at fill/finish facility j for delivery to market l in year n, raising this term to the power of 0.8 causes it, and consequently the entire model, to become nonlinear. LT_{ijl}, by contrast is a parameter rather than a decision variable, thus the exponent of 0.6 is not problematic. In addition, because we set LT_{ijl} equal to one month for all products, this term cancels and is taken out of the subsequent equations below.

In order to preserve the linearity of this model and ability to solve it using CPLEX, a methodology was developed and tested to implement the above objective function term in a linear manner. First, note that the safety stock component of the objective function (above) can be rewritten as:

[7]

$$c_{ij} \sum_{ijn} \sum_{el} \left(\frac{\left(f_{ije} * x_{ijlen} \right)^{0.8} \left(f_{ije} * x_{ijlen} \right)^{0.2}}{\left(f_{ije} * x_{ijlen} \right)^{0.2}} \right) = c_{ij} \sum_{ijn} \sum_{el} \left(\frac{f_{ije} * x_{ijlen}}{\left(f_{ije} * x_{ijlen} \right)^{0.2}} \right)$$

Although these terms are still nonlinear, note that the numerator alone of the second term is linear. Thus, the entire term can be made linear if it is rewritten as:

[8]

$$c_{ij} \sum_{ijn} \sum_{el} \left(\frac{f_{ije} * x_{ijlen}}{\left(ss^*_{ijn}\right)^{0.2}} \right)$$

[9]

where $$ss^*_{ijn} = f^*_{ije} x^*_{ijlen}$$

where f^*_{ije} is the lot size and x^*_{ijlen} is a number of lots of product *i*, size *e*, produced at facility *j* for market *l* in year *n*, under the *optimized* scenario. These terms are fixed numbers, and collectively they prevent the entire safety stock term from underestimating the other terms in the objective function once it is made linear. An analogous method to that proposed by Gebennini, Gamberini et al. (2009) in Section 3.3 was developed to handle this. We will define the array SS^* to be the set of all optimized values of ss^*_{ijn} for all *i*, *j*, and *n* (i.e. $SS^* \left(ss^*_{ijn} \epsilon SS^*\right)$). In order to determine these optimal values, we will proceed to solve this problem iteratively over multiple iterations *k*. Letting $SS^{(k)}$ $\left(ss^{(k)}_{ijn} \epsilon SS^{(k)}\right)$ be the set of all candidate solutions for the optimal set SS^* in iteration *k*, we describe this iterative approach as follows:

1. For initial iteration k=1, set $SS^{(1)}$ such that $f^{(1)}_{ije} * x^{(1)}_{ijlen} = (\min_e(f_{ije}) * 1)$ for all products *i*, facilities *j* and years *n*, and f. In other words, assume that the safety stock cost for each product-site-year combination is the equal to what it would be if only one of the smallest possible batches were made at this site each year for all markets (independent of which market it is sent to). Thus, if any product is produced in a given site-year, this initial SS^k_{ijn} will serve as the denominator. Otherwise $x_{ijlen} = 0$, and the safety stock component of this product will equal zero.
2. Solve the MILP with the array of $SS^{(k)}$ values determined in the prior step plugged into Equation [8].

3. For all products *i*, facilities *j* and years *n*, calculate $SS^{(k+1)}$ based on the actual values x_{ijlen} determined by the solution to the k^{th} iteration. For all *i*, *j*, *n*, where $\sum_{el}(x_{ijlen}) = 0$ in the k^{th} iteration, set $ss_{ijn}^{(k+1)} = ss_{ijn}^{(1)}$.

4. If $SS^{(k+1)} = SS^{(k)}$, return the solution values from the (k-1)th iteration, setting $SS^* = SS^{(k)}$, thus yielding the optimized solution. Otherwise, increment k ($k = k + 1$) and return to step (2).

The above method was first tested for accuracy and effectiveness with a sample dataset comprised of eight products, each with eight potential lot sizes, three facilities, two markets and five years. Six iterations were performed to determine the effect this approach had on both the production-distribution allocation decisions, as well as the total cost function. As can be seen in Figure 6 below, the production allocation decisions only changed minimally throughout these iterations. More importantly, Figure 7 shows how the total network cost became almost completely stable after the first iteration. This suggests that, although it requires a first iteration to set the near-optimal values in the *SS* matrix, once this has been done, minor changes in production allocation do not have a significant impact on the safety stock component of total network costs (and an even less significant impact on total network costs per se). For this reason, it was decided that two iterations will suffice to determine near-optimal safety stock costs when the model is implemented with the full set of products, facilities, markets and years.

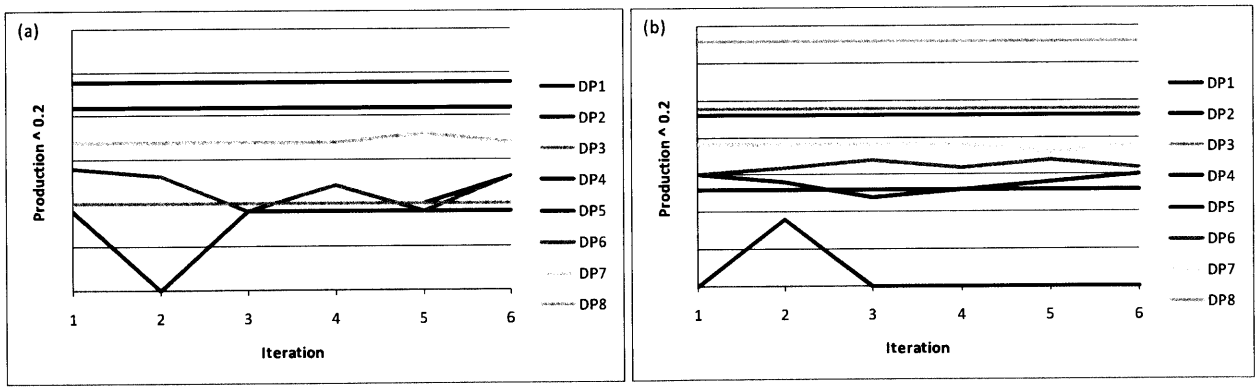

Figure 6. Production Level at Facilities A and B for Eight Drug Products ("DPs") in Sample Iterations

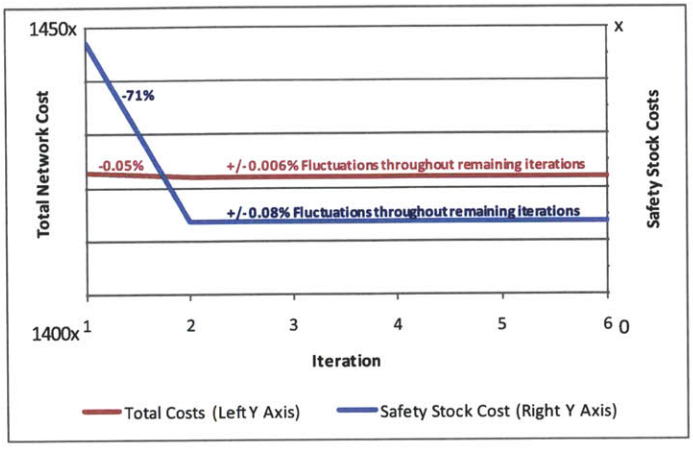

Figure 7. Safety Stock and Total Network Costs throughout Sample Iterations

4.5.2 Summary of Model Inputs

After developing an appropriate linearization of the model, the next step was to determine the appropriate factors and other inputs to run the model. As discussed in Section 4.4, factors were applied to the values of capacity and production constraints that were measured by the recent capacity audit of Site 1A. A range of values were examined for these parameters in order to understand the sensitivity of the model to each factor. In addition, various scenarios (in terms of demand level, service level, various financial/tax implications, opening/closing date restrictions for different sites, and the ability to provide low capacity staffing structures to sites) were tested in the model. In total, 40 variables were set for a given iteration, a summary of which is in Table 3 below.

Assumption / Factor	Inputs Selected in Various Scenarios		
Demand Scenario	Pessimistic	Base	Optimistic
WACC		10%	
Forecast Error Variability Factor		0.8	
Service Level	95%	99%	99.9%
DS Yield Loss per Lot		2kg	
Yield Loss Variable Cost		10%	
RMS/Site-1A Line Speeds	50%	75%	100%
RMS/Site-1A C/O Times	50%	100%	125%
Site-1B Line Speeds		500 (SYR), 600 (VI)	
Site-1B/Site-1A C/O Times	125%	150%	200%
Financial Considerations		Various Scenarios	
Low Capacity Staffing Option	Available	Not Available	

Table 3. Various Inputs Used in Different Implementations of the MILP

4.5.3 Summary of Scenarios Examined

Following the above, the model was run in IBM ILOG CPLEX Optimization Studio. Full code for the implementation of the MILP can be found in Appendix F. Seven particular runs were studied in detail as these highlight some interesting points about the model and production system.

These scenarios were chosen specifically to highlight several points that are interesting from a managerial perspective. For that reason, many of the potentially variable inputs (e.g. demand scenario, service level) were held fixed, but particular inputs were changed as indicated in Table 4 below. The scenarios were chosen to demonstrate the following:

Scenario 1: A base test case, assuming that RMS has slightly slower lines and slower changeovers ("C/O") than Site 1A or Site 1B (based on a best guess at time of analysis).

Scenario 2: A modified test case, where the line speed and C/O times are slightly worse. In addition, this model implemented the effect of a proposed 4% revenue tax that could potentially impact all product that goes through any production step at either Site 1A or Site 1B (O'Grady 2010).

Scenario 3: This scenario implements the same production assumptions as Scenario 1, but it assumes the revenue tax affects all product flowing out of Site 1A or Site 1B (i.e. there is no tax credit for U.S.-destined product).

Scenario 4: This is a "job shop specialization" scenario, whereby RMS is assumed to have significantly slower line speeds than the the facilities at Site 1A/B (25% slower), but significantly faster C/O times (50% of Site 1A, 25% of Site 1B).

Scenario 5: This is the highest financial burden scenario. In addition to the full amount of revenue tax at Site 1A/B, this scenario assumes a 10% tax on profits attributable to product formulated and filled at RMS.

Scenario 6: This scenario removes all of the financial burdens and assumes that RMS is able to operate in a low capacity mode, where facility staffing arrangements could be flexible and total staff costs could be reduced.

Scenario 7: This scenario is modeled exactly after the base case inputs of Scenario 1. The only difference between the two is that the RMS Minimum Production constraint was removed from the CPLEX model.

Scenario	**1**	**2**	**3**	**4**	**5**	**6**	**7***
Operating Assumptions							
RMS Avg Line Speed (% of APR-1)	90%	50%	90%	25%	90%	90%	90%
Changeover Time (% of APR-1)							
RMS	1.25	1.75	1.25	0.5	1.25	1.25	1.25
Site 1A	1	1	1	1	1	1	1
Site 1B	1.25	1.75	1.25	2	1.25	1.25	1.25
Enable Low Capacity Option	0	0	0	0	0	1	0
Financial Assumptions							
Include Tax on RMS Profits	0	0	0	0	10%	0	0
Include APR Tax on NACO Revenues	0	0	1	0	1	0	0
Include APR Tax on ICO Revenues	0	1	1	0	1	0	0

*RMS Minimum Production Constraint removed for this scenario

Table 4. Inputs for Various Scenarions Examined in MILP Model

Per the approach discussed in Section 4.5, each of these scenarios was run once with an initial default set of *SS* values, and then a second time with specific *SS* values as determined in the first run. Typically, this practice would lead to overall safety stock costs decreasing by approximately 50% in the second iteration, but with other costs, as well as production allocation decisions, relatively unchanged. The data discussed in Chapter 5 below is the output of the second iteration, in all cases.

4.5.4 Model Interface

Aside from the seven scenarios discussed in this thesis, the goal of the internship was to create a flexible model that will enable Amgen to optimize production allocation across their network under various sets of assumptions and constraints. Section 4.5.2 and Appendix D discuss the parameters that

can be set for these constraints, but the purpose of this section is merely to give an example of how data can be fed into and extracted from the MILP running in IBM ILOG CPLEX Solver.

Shown below, Table 5 and Table 6 are example sets of data that are plugged into four different queries within the source database that the CPLEX Solver will read from. This is a Microsoft Access Database, and also includes all of the underlying cost, capacity and production requirements data (collected from various sources at Amgen), as well as all of the logic and data-preprocessing steps (calculated within the database by multiple queries) to prepare the final set of data for the Solver.

Scenario	1	2	3	4	5	6	7	8	9	10	11
Demand Scenario	Base	Base	Base	Base	Base	Base	Base	Base	Optimistic	Pessimistic	Base
WACC	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
r_ij	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Z_service_level	2.33	2.33	2.33	2.33	2.33	2.33	2.33	2.33	2.33	2.33	2.33
eta_YieldLoss_kg	2	2	2	2	2	2	2	2	2	2	2
eta_YieldLoss_AG_factor	1	1	1	1	1	1	1	1	1	1	1
eta_YieldLoss_Var_factor	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
bCalc_tau_Factor	1	1	1	1	1	1	1	1	1	1	1
bCalc_WAvgFFCost_Factor	0.05	0	0	0	0	0	0	0	0	0	0
tauCalc_WAvgBulkCost_Factor	0.05	0	0	0	0	0	0	0	0	0	0
RMS_Site-1A_zeta_Factor	0.9	0.9	0.75	0.5	0.9	0.9	0.9	0.9	0.9	0.9	0.25
RMS_Profit_TaxPct	0	0	0	0	0	0.1	0.1	0	0	0	0
Site-1_Tax_on_NACO_bool	0	0	0	0	1	1	0	0	0	0	0
Site-1_Tax_on_ICO_bool	0	0	0	1	1	1	1	0	0	0	0
Enable_Low_Capacity_Option	0	0	0	0	0	0	0	1	1	1	0

Table 5. Universal Variables Input into MILP Model

Table: jn_Boolean

j	n	Available?
RMS	2013	0
RMS	2014	1
RMS	2015	1
RMS	2016	1
RMS	2017	1
Site-1A	2013	1
Site-1A	2014	1
Site-1A	2015	1
Site-1A	2016	0
Site-1A	2017	0
Site-1B	2013	0
Site-1B	2014	1
Site-1B	2015	1
Site-1B	2016	1
Site-1B	2017	1

Table:j

j	ijs_CO_time_factor
RMS	1.25
Site-1A	1
Site-1B	1.25

Table: n

n	APR_Rev_TaxPct
2013	0.0275
2014	0.025
2015	0.0225
2016	0.01
2017	0

Table 6. Facility-Specific Variables Input into MILP Model

The output of the model is just as important to the usability of this tool to Amgen. The CPLEX Solver writes raw data (decision variable outputs and objective function calculations) to the Excel spreadsheet specified in the *.dat* file (See Appendix F for an exact specification of this file). However this information is not very useful for managerial analysis in this form. To make this data more readable, we wrote a macro in Visual Basic for Applicatoins ("VBA") that would automatically perform multiple calculations on the raw data and output a Pivot Tables containing a presentation of data that is more useful to management. Table 7 below presents a sample final output with production allocation data (obfuscated). In addition to this, we the VBA scripts produced an output of total networks cost broken down by planning year (2013-2017) and type of cost (staff, setup, material, tax, holding costs, etc.). We chose not to show an example of this output as the format is trivial and the data would have to be obfuscated.

% of Global Demand by Product Filled at RMS — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017
Drug 1	0%	3%	5%	8%	9%
Drug 2	0%	15%	20%	22%	22%
Drug 3	0%	65%	63%	105%	37%
Drug 4	0%	65%	50%	37%	40%
Drug 5	0%	0%	0%	0%	0%
Drug 6	0%	3%	3%	3%	4%
	0%	0%	0%	0%	0%

Facility Staffing Structure by Year — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017
⊟RMS					
5x24x1Rx1S		1	1	1	1
⊟Site-1B					
5x24x1Rx1	1	1	1		1
5x24x2Rx0S				1	

[Value of "1" means given shift structure is selected at site in given year]

Facility Utilization by Year — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017
RMS	0%	25%	23%	22%	21%
Site-1A	0%	0%	0%	0%	0%
Site-1B	100%	64%	58%	42%	47%

Unit Production by Facility, Presentation & Year — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017	Grand Total
⊟RMS						
SYR						
VI						
⊟Site-1B						
SYR						
VI						
Grand Total						

Average Lot Size by Fill Facility and Year* — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017	Grand Total
RMS		96,919	93,472	86,347	87,133	90,917
Site-1B	104,556	121,618	122,279	116,459	127,295	117,288
Grand Total	**104,556**	**110,490**	**109,300**	**102,860**	**108,553**	**107,248**

Comparison of Average Lot Sizes*

	2013	2014	2015	2016	2017
Site-1B/RMS		125%	131%	135%	146%

*Unweighted average; based on number of lots only

# of Batches by Facility, Presentation & Year — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017	Grand Total
⊟RMS						
SYR						
VI						
⊟Site-1B						
SYR						
VI						
Grand Total						

Avg Batch Size by Facility, Presentation & Year — *OBFUSCATED DATA*

Row Labels	2013	2014	2015	2016	2017	Grand Total
⊟RMS						
SYR		107,975	102,085	89,771	91,091	97,582
VI		81,312	81,312	81,312	81,312	81,312
⊟Site-1B						
SYR	86,599	88,637	89,165	87,092	96,141	89,283
VI	135,634	198,575	199,543	186,941	195,835	177,208
Grand Total	**104,556**	**110,490**	**109,300**	**102,860**	**108,553**	**107,248**

Comparison of Average Lot Sizes*

	2013	2014	2015	2016	2017
Site-1B/RMS					
SYR		82%	87%	97%	106%
VI		244%	245%	230%	241%

*Unweighted average; based on number of lots only

Table 7. Sample Output from MILP Model, as Formatted in Excel

5 Results and Recommendations

After running the model under various scenarios with a range of input assumptions, we examined and compared the resulting production/distribution allocation solutions and total network costs. From this data, we distilled four key findings:

(1) depending on the model inputs, variable staffing costs and financial costs were the two most predominant factors, but financial costs were most sensitive to assumptions,

(2) despite the large impact of staffing costs, there was typically some amount of excess capacity in the network,

(3) the fact that staffing and fixed costs led the model not to staff the RMS facility in the one scenario (7) where is was not explicitly required suggests that the decision to bring RMS online could be generally attributed to risk mitigation or network expansion rather than only to network cost optimization, and

(4) batch sizes selected at RMS tended to be smaller than those selected elsewhere.

In response to these findings, we developed the following three recommendations to Amgen Inc.:

(1) the tax implications of all product flows should be incorporated into the final production/distribution allocation decisions,

(2) it is important to create flexible staffing arrangements/options for the formulation/fill facilities in order to control total variable network costs and capacity utilization going forward, and

(3) RMS should be optimized for more, smaller batches (when making scheduling or CapEx decisions) as the model tends to allocate smaller batches for both vial and syringe products to RMS.

These findings and recommendations are discussed in detail below.

5.1 Magnitude of Staffing Costs and Financial Costs in Model

Perhaps the most salient finding from the seven examined scenarios is how staffing costs and financial costs dominated total variable network costs captured in the model. As shown in Figure 8 below, staffing costs accounted for approximately 50-90% of total variable network costs. Additionally, regardless of scenario, it is interesting to note that these costs were fairly constant. In fact, in the first five scenarios, these costs stayed within 4% of their average. Costs were considerably lower for Scenario 6 (32% below this average), in which a low capacity option was implemented at RMS, and Scenario 7 (48% below this average), in which the minimum flow constraint to RMS was relaxed.

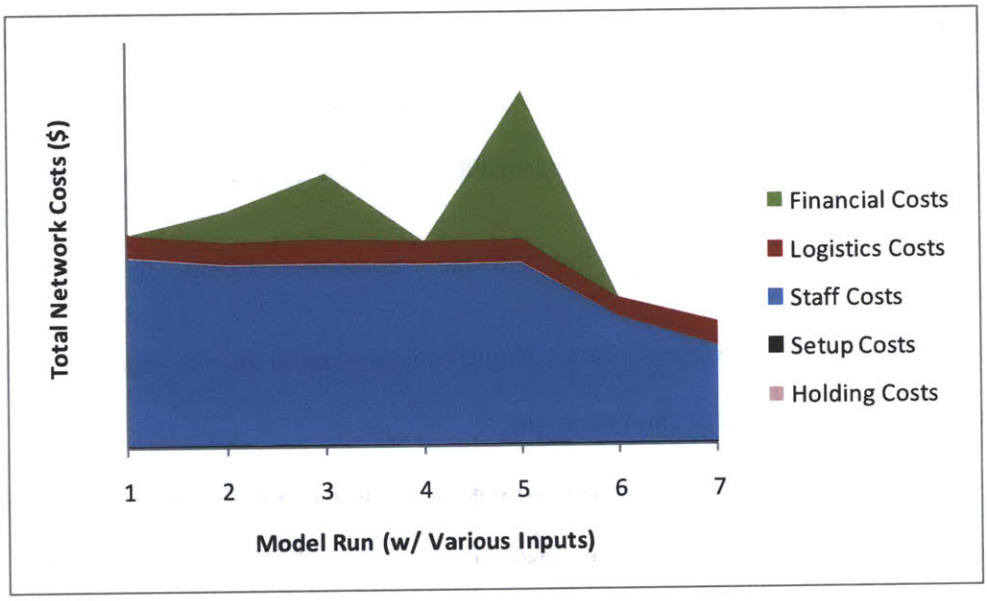

Figure 8. Total Variable Network Costs by Cost Component under Various Scenarios

Similar to staffing costs, financial costs play a very important role in several of the scenarios examined. Unlike staffing costs, however, financial costs are much more sensitive to the assumptions that are used to develop a given scenario. Thus, management should take care to fully understand the financial impact of any production allocation or distribution decisions, as these could have a major impact on total variable costs.

Additionally, we can see from Figure 8 that, overall, logistics costs typically range from 7-12%, or slightly higher in Scenario 7. Thus, we can see evidence from this model that the biopharmaceutical industry follows the concept of high value densities as discussed in the analysis of Cooper (1993) in Section 3.2.

Even more dramatically, setup cost and aggregate holding costs (cycle inventory + safety stock), despite the care we took to accurately estimate these items, are overshadowed by staffing and financial costs.

5.2 Staffing Costs and Flexible Capacity

Although one might consider the appropriate tax assumptions as exogenous inputs over which Amgen has no control, the same is not necessarily true for staffing costs. By contrast, staffing costs are both the largest most consistent total variable network cost component, and also that over which Amgen might exercise the greatest amount of control.

Because of this fact, the second piece of information studied in the resulting data from the seven scenarios was capacity utilization. As shown in Figure 9 below, the average capacity utilization (during active years) for the three facilities is highly dependent on the chosen scenario. For RMS, capacity utilization is likely to be very dependent on at least two factors:

(1) the production metrics (e.g. line speed and C/O time) specified at RMS, and

(2) the amount of total production allocated by the model to RMS (assumption).

As we can see in Figure 10 below, which shows the amount of production for each DP type and all products at RMS under each scenario, the full percentage of maximum allowable production (a value was assumed) was allocated to RMS under Scenarios 1-4. Presumably tax considerations caused this amount to decrease from the maximum allowable in Scenarios 5 and 6, and in Scenario 7, in which RMS was not utilized.

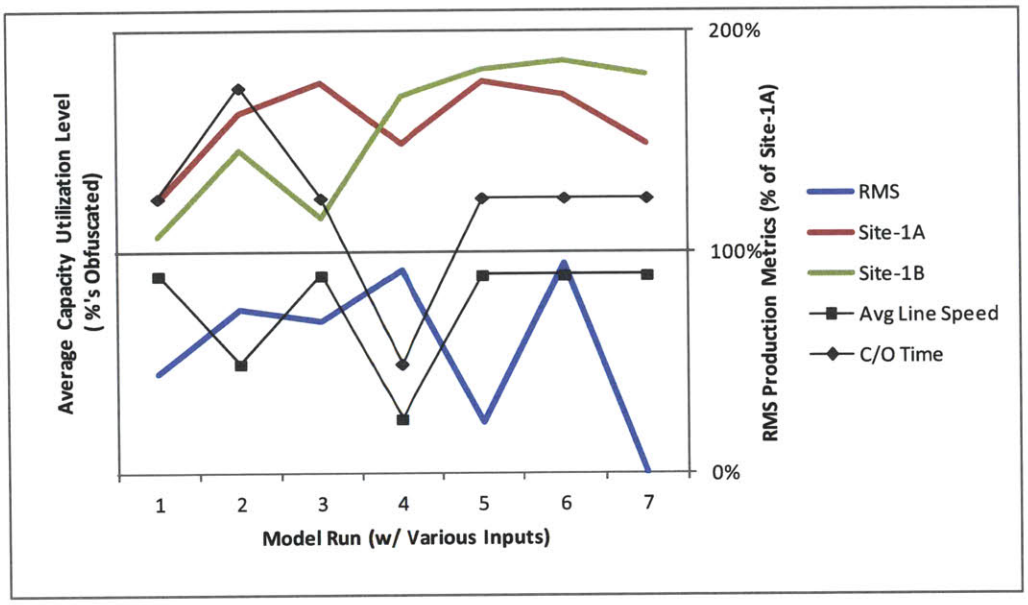

Figure 9. Capacity Utilization and RMS Production Metrics under Various Scenarios

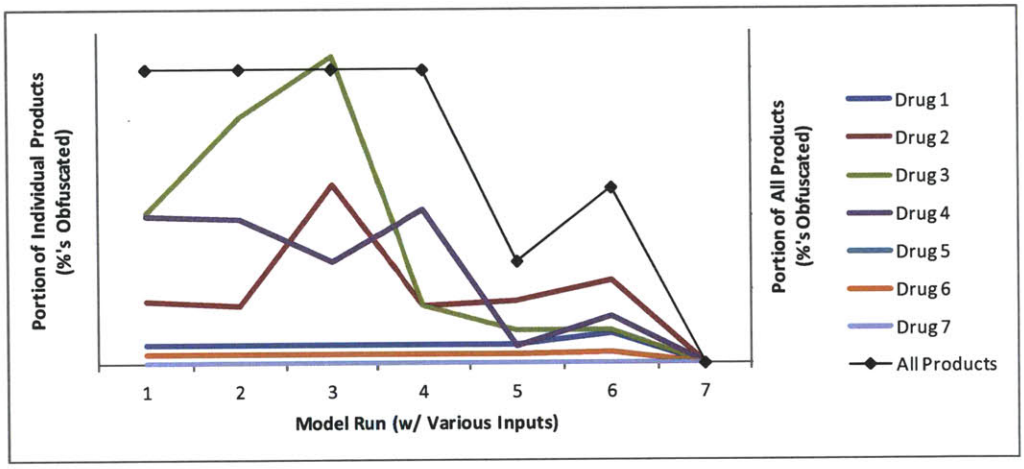

Figure 10. Production at RMS by Drug under Various Scenarios

Comparing Figure 10 with Figure 9, one can see that varying production metrics between Scenarios 1- 3 (during which RMS produced the maximum allowed amount of global product) led to slight changes in overall utilization. A more dramatic change in the production metrics was implemented in the "job shop"

specifications of Scenario 4, in which the capacity utilization at RMS spiked because of the slow line speeds, despite the very quick C/O times, assumed in this hypothetical scenario.

Despite these varying levels of capacity utilization at RMS in Scenarios 1-4, total staffing costs, as shown in Figure 8 remain constant. Together these facts suggest that the minimum capacity option, as currently defined and selected by the model, is sufficient to meet the assumed hypothetical production demand at RMS. This premise is further supported by Scenario 6, in which a hypothetical low capacity option is implemented at RMS. The results show a sharp increase in capacity utilization at RMS, and a significant decrease in total network costs due to savings in staffing costs. For these reasons, it is recommended that management consider any opportunities that may exist to create flexible staffing options at RMS.

It is worth further examining the underlying reasons that cause flexible staffing options to be more effective than facility design/equipment selection in reducing total network costs. In the proposed cost model, which reflects Amgen's global variable network costs, there are significant step functions with respect to staffing costs. These are illustrated conceptually in the in Figure 11, an exemplary diagram of how various cost components change as a function of production level. Some costs, such as logistics costs or tax costs, can be considered truly variable because they increase incrementally with each additional unit of production. By contrast, staffing costs, which comprise up to 90% of the *variable* costs of the model, are only variable in the long run. As shown in Figure 11, this is because these costs hardly change at all until specific production thresholds are crossed.[6] Beyond each threshold, additional capacity is required, so a major cost is incurred to step up to the next shift structure level. By the same logic, any production time savings will not carry to the bottom line unless they result in a step function decrease in a facilities staffing level. However, at the same time that large increases or decreases in capacity utilization can have no effect when a company is in the middle of a staffing cost plateau between step function,

[6] This is analogous to the capacity options proposed by Corsano and Montagna (2011) and discussed in Section 3.3, and the same logic is followed in the capacity constraints of the MILP model formulated in Section 4.3.

being near a step up or down can cause incremental capacity consumption to have a large financial impact.

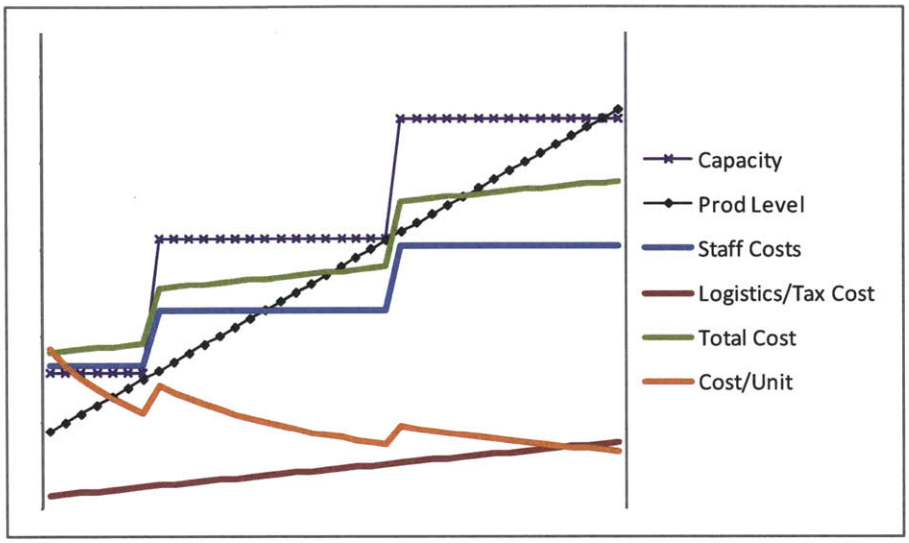

Figure 11. Costs as a Function of Production Level

5.3 New Site Creates Value by Mitigating Risks, Adding Flexibility

Scenario 7 points to the relationship between capacity, network resilience, and total costs. In this scenario, we relaxed the minimum production constraint for RMS (discussed in Section 4.3.5.6) which requires RMS to formulate and fill at least one batch of every product in every year. The purpose of this constraint was to ensure that, once online, RMS would retain sufficient expertise and training to be able to ramp up to 100% of global formulation/fill operations within 3 months of an adverse event that disrupted production elsewhere. Once this constraint is relaxed, however, RMS is not brought online. Total network costs are reduced, but so is total network capacity as well as the fundamental resilience of the network, since it would result in the geographic concentration of formulation/fill activities at Site 1A/B.

Based on this analysis, we can derive the conclusion that RMS fulfills risk mitigation rather than only a network logistics cost optimization function for Amgen. As we can see in Figure 8, the total variable

network costs in Scenario 7 are somewhat lower than the corresponding costs in other scenarios. It is worth noting that these results: (i) are still significantly impacted by the financial/tax assumptions (partially irrelevant to the fixed cost of bringing RMS online), and (ii) represent variable costs which are also only a portion of the total network costs (also comprised of a more significant fixed portion). Nonetheless, in contrast to supply chains where the lower value densities described by Cooper (1993) might cause logistics costs to drive more of the optimization, the high upfront cost of bringing RMS online is not significantly offset by lower outbound logistics costs. However, the additional cost of bringing RMS online could be attributed to both the level of insurance and resilience provided to Amgen's supply chain as well as the expanded capacity that might enable global expansion, both means by which Amgen might continue to "ensure continuity of supply" as the Wall Street Journal article suggested (Gryta 2011).

5.4 Batch Sizing and Small Batch Specialization at RMS

Because capacity utilization and efficient facility operation can have a large financial impact near the staffing step function points, it is worth noting ways in which this model can inform facility design. In these situations where a facility may be close to capacity under its current shift structure, facility efficiency and production metrics can become very important.

With respect to facility design, the key finding from the seven scenarios was that, in general, the batch or lot sizes selected by the model at RMS were much smaller than those selected at Site 1A or Site 1B. Figure 12 below shows the ratio of average batch size at Site 1B to that at RMS, for each presentation type. Average vial batch sizes at Site 1B range from 140 to 250% of the averages at RMS in different scenarios. Average syringe batch sizes are even more dramatic, ranging from slightly smaller than RMS averages to over 300% in size.

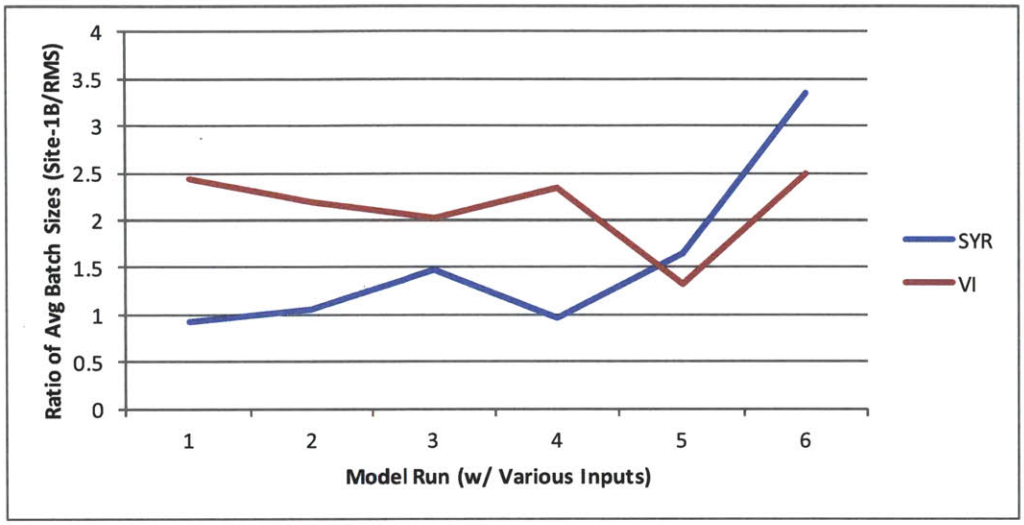

Figure 12. Comparison of Average Batch Sizes (Site 1B/RMS)

The nature of demand in ICO markets leads to two possible drivers of this phenomenon: (1) that demand is typically for smaller quantities of product and (2) that demand typically calls for longer remaining shelf lives, which in turn will drive up the required production frequency and drive down the average batch sizes. Regardless of the reason for this outcome, the clear trend in the data suggests that it might be reasonable to consider specializing equipment, staffing and training at RMS for a high mix, low volume (HMLV) mode of operation.

6 Conclusion

6.1 Next Steps and Opportunities for Further Research

The goal of this thesis was not only to create a set of recommendations for Amgen regarding the production allocation decisions related to the newly-acquired formulation/fill facility, it was also to develop a methodology and tool with which these decisions could be made under various future scenarios. Thus, although this research draws its own conclusions, it is also hoped that this will create the opportunity for greater integration of this approach in the execution of planning decisions at Amgen.

Notwithstanding the above, there are some clear challenges to implementing a somewhat complex MILP such as the one described in this thesis in the managerial context where little or no prior use of linear programming for decision support existed. This is not a novel challenge. In a two-decade review of the evolution of such systems that is now itself 15 years old, Geoffrion and Powers(1995) conclude that:

> optimization-based software for designing distribution systems has been slower than heuristic software to migrate from mainframe to desktop and slower to develop graphic user interfaces. Nowadays, logistics executives nearly always choose desktop analytical software over mainframe software and a GUI over an older style interface, even if it means accepting a heuristic rather than optimizing package.
>
> Other factors include discomfort with "high" technology when easily understandable "low" technology appears adequate, inadequate managerial appreciation of the added benefits of optimization, difficulties in reliably obtaining optimal solutions using commercial optimization software, and the lingering memory of past failed attempts to do optimization.

It is possible that all of these influences against the use of optimization, as well as the natural tendency to prefer the analysis that you can fully understand or that could be repeated ad hoc with tools such as Excel, will limit the proliferation of this approach at Amgen. Although this will not pose a major challenge in today's competitive environment, it may in the future when there is a greater amount of competition from substitute drugs or *biosimilars* and Amgen is in a position to compete on operational efficiency as well as

drug development and intellectual property. Hopefully the tools and methods suggested in this paper will be reexamined or perhaps taken closer to broad implementation by another LGO Fellow between now and that time.

6.2 Conclusion

This thesis presents a rigorously formulated MILP that aims to closely mimic the costs, constraints, and behavior of the new production system Amgen will have once it brings the RMS and Site 1B online. The model is specifically designed to capture the cost of different shift structures at different sites, the tradeoff between lot size and total capacity, tax implications of various scenarios, network logistics costs and other items that will drive the total cost function of Amgen's production allocation and distribution decisions.

This model was populated with a mix of actual and hypothetical data based on the best available information at the time of publishing, and it was run with multiple input assumptions supplied by the author to see the impact of various hypothetical operational or financial scenarios on Amgen's total costs. From these scenarios, three recommendations were distilled: Amgen should pay close attention to the potential financial implications of different production allocation decisions; opportunities for flexible capacity should be examined at all sites; and equipment and infrastructure should be selected to support high mix, low volume operations at the RMS.

7 References

Amgen, I. (2009). Amgen Inc. 2009 Annual Report. Thousand Oaks, CA, Amgen Inc.

Amgen, I. (2009). An Introduction to Biotechnology. Thousand Oaks, CA, Amgen Inc.: 46.

Amgen, I. (2011). Amgen Inc. Fact Sheet. Thousand Oaks, CA, Amgen Inc.

Arntzen, B. C., G. G. Brown, et al. (1995). "Global Supply Chain Management at Digital Equipment Corporation." Interfaces **25**(1): 69-93.

Beamon, B. M. (1998). "Supply chain design and analysis: Models and methods." International Journal of Production Economics **55**(3): 281-294.

Bhatnagar, R., P. Chandra, et al. (1993). "Models for multi-plant coordination." European Journal of Operational Research **67**(2): 141-160.

Brown, G. G., G. W. Graves, et al. (1987). "Design and Operation of a Multicommodity Production/Distribution System Using Primal Goal Decomposition." Management Science **33**(11): 1469-1480.

Coffey, S. (2008). "Achieving Business and Operational Excellence in the Pharmaceutical Industry." MIT Leaders for Manufacturing Thesis.

Cohen, M. A. and H. L. Lee (1988). "Strategic Analysis of Integrate Production-Distribution Systems: Models and Methods." Operations Research **36**(2): 216.

Cohen, M. A. and S. Moon (1991). "An integrated plant loading model with economies of scale and scope." European Journal of Operational Research **50**(3): 266-279.

Cooper, J. C. (1993). "Logistics strategies for global businesses." International Journal of Physical Distribution & Logistics Management **23**(4): 12.

Corsano, G. and J. M. Montagna (2011). "Mathematical modeling for simultaneous design of plants and supply chain in the batch process industry." Computers & Chemical Engineering **35**(1): 149-164.

Coyle, D. (2011). Amgen acquisition to secure 280 jobs. Irish Times

Gebennini, E., R. Gamberini, et al. (2009). "An integrated production-distribution model for the dynamic location and allocation problem with safety stock optimization." International Journal of Production Economics **122**(1): 286-304.

Geoffrion, A., G. W. Graves, et al. (1973). Multicommodity Distribution System Design by Benders Decomposition. Ft. Belvoir, Defense Technical Information Center.

Geoffrion, A. M. and R. F. Powers (1995). "Twenty Years of Strategic Distribution System Design: An Evolutionary Perspective." Interfaces **25**(5): 105-127.

Gryta, T. (2011). Amgen To Purchase Pfizer Manufacturing Plant In Ireland. The Wall Street Journal. New York, Dow Jones.

Hardy, R. (2010). "Evaluation of Marking Technology for Risk Management in the Biopharmaceutical Supply Chain." MIT Leaders for Global Operations Thesis.

Hodder, J. E. and M. C. Dincer (1986). "A multifactor model for international plant location and financing under uncertainty." Computers & Operations Research **13**(5): 601-609.

Hunnicutt, L. A. (2008). "Investigating Late Stage Biopharmaceutical Product Loss Using Novel Analytical and Process Technology." MIT Leaders for Manufacturing Thesis.

Jay, W. G. W. (2009). "Application of Lean and Continuous Improvement Methodologies at a Biopharmaceutical Manufacturing Site." MIT Leaders for Manufacturing Thesis.

Kristinsdóttir, Á. (2008). "Capital Project Development in the Biotechnology Industry." MIT Leaders for Manufacturing Thesis.

Lee, J. (2010). "Developing Biotechnology Company's Future Positioning Strategy in Prefilled Syringe Market." MIT Leaders for Global Operations Thesis.

Lehman, R. J. (2010). Site 1A Capacity Audit: Peter Pick Interview Notes (11/15/2010). Thousand Oaks, CA, Amgen Inc.

Matthew, J. (2009). "Developing the Business Case for Quality by Design in the Biopharmaceutical Industry." MIT Leaders for Manufacturing Thesis.

Miller, G. A. (2006). Retrieved 3/12, 2011, from http://wordnetweb.princeton.edu/perl/webwn?s=biotechnology.

O'Grady, M. A. (2010). Puerto Rico's Governor Channels Ronald Reagan. The Wall Street Journal. New York, NY, Dow Jones & Co., Inc.

Pasenek, D. M. (2008). "The Conclusion of a Biologic's Lifecycle: Manufacturing Sourcing Strategies on the Eve of Follow-on Biologics." MIT Leaders for Manufacturing Thesis.

Peidro, D., J. Mula, et al. (2009). "Quantitative models for supply chain planning under uncertainty: a review." International Journal of Advanced Manufacturing Technology **43**(3-4): 400-420.

Rosenfield, D. B. (1994). Demand Forecasting. The logistics handbook. J. F. Robeson, W. C. Copacino and R. E. Howe. New York Toronto, The Free Press ; Maxwell Macmillan Canada ; Maxwell Macmillan International**:** 327-351.

Sekar, S. (2010). "Developing a Framework for Global Distribution in the Biopharmaceutical Industry." MIT Leaders for Global Operations Thesis.

Shi, Y. and M. Gregory (1998). "International manufacturing networks--to develop global competitive capabilities." Journal of Operations Management **16**(2-3): 195-214.

Thanh, P. N., N. Bostel, et al. (2008). "A dynamic model for facility location in the design of complex supply chains." International Journal of Production Economics **113**(2): 678-693.

Thomas, D. J. and P. M. Griffin (1996). "Coordinated supply chain management." European Journal of Operational Research **94**(1): 1-15.

Tsiakis, P. and L. G. Papageorgiou (2008). "Optimal production allocation and distribution supply chain networks." International Journal of Production Economics **111**(2): 468-483.

Tsiakis, P., N. Shah, et al. (2001). "Design of multi-echelon supply chain networks under demand uncertainty." Industrial & Engineering Chemistry Research **40**(16): 3585-3604.

Vaudant, J. (2008). "Evaluation of Drying Technologies for Storage and Shipment of Recombinant Protein Drug Substance." MIT Leaders for Manufacturing Thesis.

Vega González, M. A. (2009). Stock Level Optimization at the Distribution Center through Improved Supply Management Practices. MIT Leaders for Manufacturing Thesis. Cambridge, MA, Massachussetts Institute of Technology**:** 117.

Vidal, C. J. and M. Goetschalckx (1997). "Strategic production-distribution models: A critical review with emphasis on global supply chain models." European Journal of Operational Research **98**(1): 1-18.

Villa, A. D. (2008). "Lean Transformation Methodology and Implementation in Biopharmaceutical Operations." MIT Leaders for Manufacturing Thesis.

Wikipedia (2011). CPLEX -- Wikipedia, The Free Encyclopedia.

Zhang, A., G. Q. Huang, et al. (2009). A Mixed Integer Programming Model to Evaluate the Impact of Business Factors on Global Manufacturing Relocation Decisions. New York, Ieee.

Appendix A. Safety Stock Factor Calculation

In order to determine the appropriate level of safety stock (to calculate annual holding costs of this stock), it is necessary to establish a relationship between aggregate demand, time and forecast errors. As explained in Rosenfield (1994), this relationship is characterized by the following generalized power rule:

$$\sigma_{T,D} = K\, T^{\alpha} D^{\beta}$$

where

$\sigma_{T,D}$ = forecast error for a given product as a function of the length of time period T and expected demand level D

α,β = parameters of relationship

Demand and forecast information were collected for the period of August 2008 forward in order to estimate both parameters. The collected information represents the majority of Amgen's total demand, accounting for 71 of 77 DP SKUs and 482 of 556 FDP SKUs (representing 93% of total annual demand in both cases, in September 2008).

Using 13 forecasts made between 8/1/2008 and 11/1/2009 (matched against actual demand), forecast errors and their collective standard deviation were calculated for each product at the DP and FDP levels. It is important to note that demand and forecasts were aggregated over a six-month period for the DP level, and a one-month period for the FDP level. These selections were based on the average lead time for production of each product's component. The bulk manufacturing of additional drug substance ("DS") to produce more DP is an involved process that can require six months due to bulk manufacturing schedules. FDP, however, only requires IDP as a component –the lead time for this can safely be assumed to be one-month accounting for the FF process and the fact that a significant amount of product is held in the DS stage (over 99.99% service level, causing this lead time to be independent of DS production).

Average demand over the same time periods (six months for DP, one month for FDP) was then calculated using monthly demand data from September 2008 to December 2009. The natural log of

forecast error and average demand for each SKU were yielded and results were sorted by ln(Average Demand), and then plotted $\sigma_{forecast\ error}$ against μ_{demand} at the DP and FDP level separately. These results were then plotted and a linear regression was performed for each graph yielding the β paremters of 0.77 at the DP level and 0.82 at the FDP level. The results of these graphs and plots are below.

The FDP result is more relevant to the situation studied in this these, as safety stock would be held at the DP or FDP stage, and re-ordering is equivalent to filling additional batches of DP and inspecting (typical lead time for this process is one month). Thus we will round and set β=0.8 for purposes of the model.

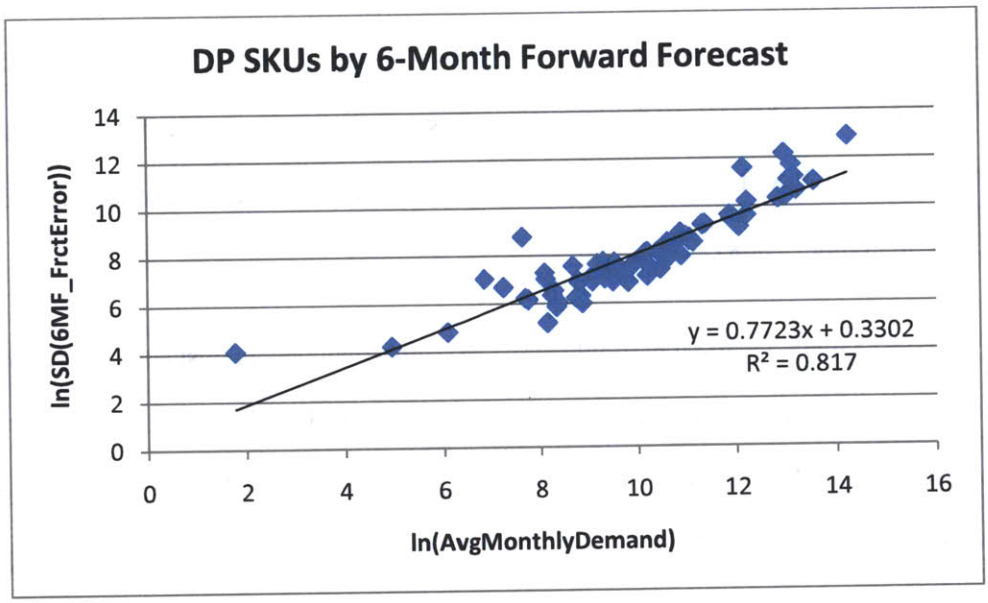

Figure 13. β-plot for Drug Product Components

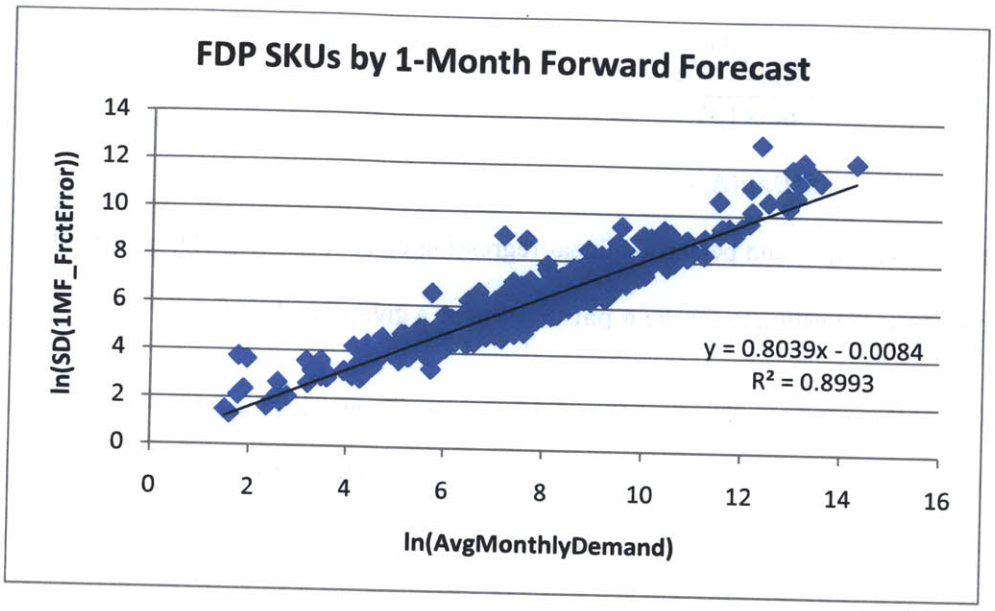

Figure 14. β-plot for Finished Drug Product

Determining the α parameter was somewhat more involved. This situation was analogous to that discussed in Vega González (2009), and thus a similar approach was followed for each product family:

1. Where p are time periods with available sales and prior forecast data, define the integer interval[7] for samples $1 \leq Y \leq w \leq \frac{\max(p)}{2}$

2. Calculate the demand (D) and forecast error (Δ) within all sample periods of length I:

$$D_i = \sum_{\hat{p}_i}^{\hat{p}_i+I} D_p \ \ where\ \hat{p}_i = (\hat{p}_{i-1} + I)$$

$$\Delta_i = \sum_{\hat{p}_i}^{\hat{p}_i+I} \Delta_p \ \ where\ \hat{p}_i = (\hat{p}_{i-1} + I)$$

3. Calculate the mean period demand (μ_I) and period forecast error standard deviation (σ_I):

[7] Vega González proposed max(p)/2 as the upper limit. In this thesis, w was set to some number of iterations such that the length of each period ($w*p$) was at least as long as the lead time for the FDP and so as to maximize the R^2 value of the regression described on the following page.

$$\mu_I = \frac{I \sum_{i=1}^{I} D_i}{\max(p)}^{\max(p)}$$

$$\sigma_I = StDev(\Delta_i)$$

4. Plot $ln(\mu_I)$ vs. $ln(\sigma_I)$ and perform a linear regression on the plot. The slope of this linear regression is the estimate for the α parameter for a given product family.

The results of this analysis, shown in Figure 15 on page 72 reveal some interesting properties of the different families of drugs. Drugs 1 through 5 are all mature products, and have high R^2 values (0.91-0.99, average=0.96) and low α parameters of 0.36-0.74 (average=0.57). On the other hand, drugs 6 and 8 are much newer products and consequently show high variability based on time, with high R^2 values (0.99 in both cases) supporting α estimates of 0.91-0.92. Drug 7 is a different type of molecule and seem to have a somewhat cyclical trend in forecast errors and was ignored for both reasons. As this study focuses on long-term strategy, 0.6 is selected as a conservative estimate for mature drugs.

After determining that forecast errors are related to time and demand with the respective parameters of α=0.6 and β=0.8, the final step is to calculate the value of K that should hold approximately for all Amgen products. We know that a reasonable model for uncertainty for a variety of lead times and demand levels is:

[10]

$$\sigma_{T,D} = K\, T^{\alpha} D^{\beta}$$

and thus

[11]

$$K = \frac{\sigma_{T,D}}{T^{\alpha} D^{\beta}}$$

and from the above-described analysis of α and β, we found the appropriate equation for demand of drug product/inspected drug product (DP/IDP) in Amgen's production process to be:

[12]

$$K = \frac{\sigma_{T,D}}{T^{0.6} D^{0.8}}$$

Using data from a variety of different drugs and assuming lead times of one-two months, K was calculated according to Equation [12]. Although we developed this model in a robust manner to handle a variety of lead times, we determined that in almost all cases, the typical lead time for the formulation/fill step (i.e. the lead time that a distribution center ordering product would encounter) was equal to approximately one month (twenty business days) for all products. Thus $T=1$ in Equation [12] causing this factor to become irrelevant. Plugging empirical data from various products into the other terms of Equation [12] leads to a range of results for K varying from 0.34 to 1.88. Of these results, we found K=0.8 to be a best approximation to represent the behavior of demand and forecast errors for most drugs and thus used this value in the MILP model.

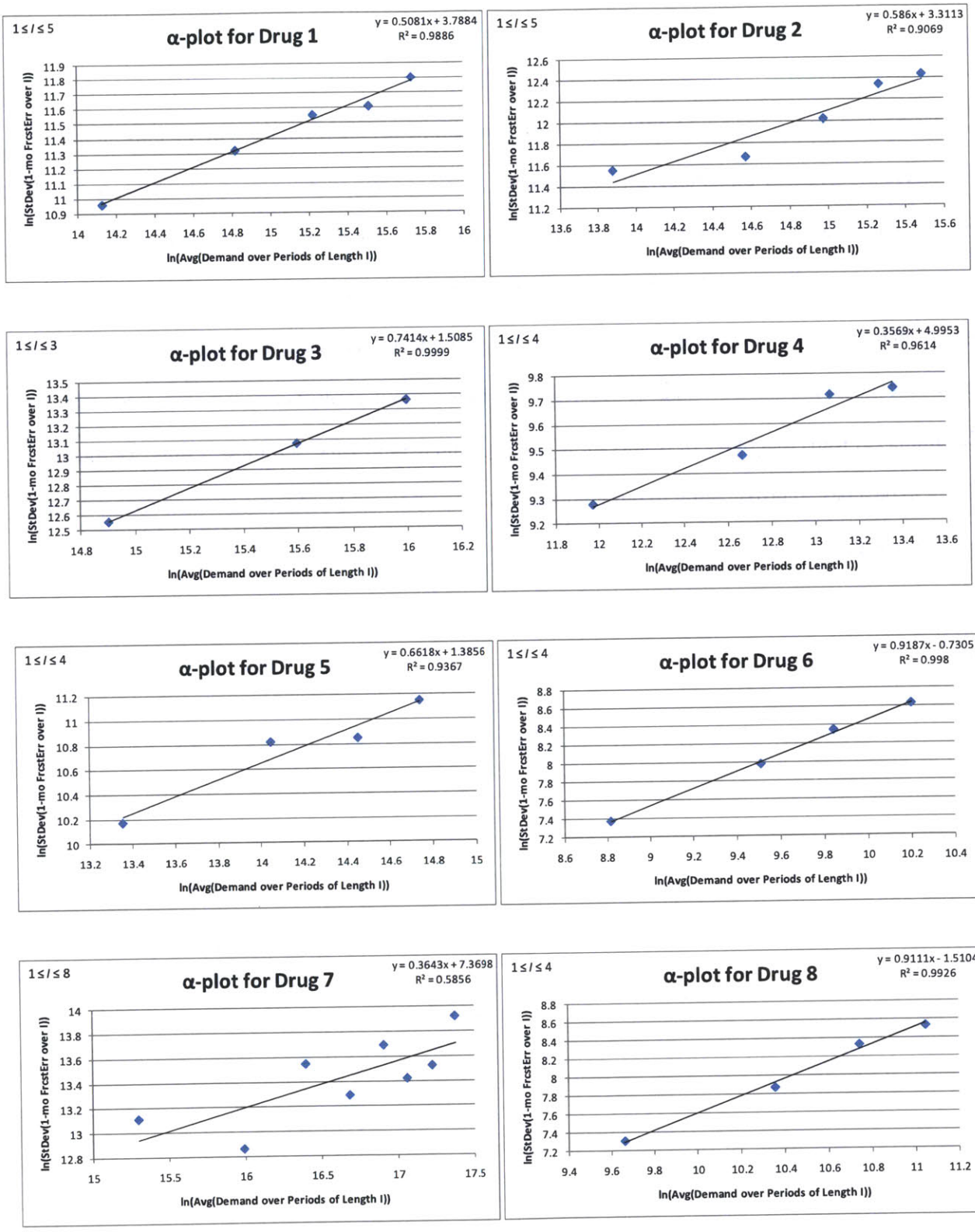

Figure 15. α-plots for Major Product Families

Appendix B. Detailed Capacity Methodology

Established capacity (Ψ_{jsn}) is a decision variable representing the number of shifts (or shift structure, s) scheduled at each FF facility j in each year n. Each option also has a corresponding annual cost indicated by the parameter π_{jsn}.

The capacity decision also leads to hours available (or φ_{jsn}) which is treated as a resource consumed by production. This parameter represents hours available for production after any reductions for scheduling, planned downtime or OEE (with the exception of changeovers).

Two production activities consume the hours available indicated by a chosen shift structure: setups and line run time. Correspondingly, rate of consumption is indicated by the following two parameters:

- Lot setup time, or ξ_{ijs}: the hours consumed for line clear, sanitization and setup for each lot of product i produced at facility j, given shift structure s.
- Line run speed, or ζ_{ij}: the units per minute at which product i can be produced at facility j.

It is worth noting that lot setup time, ξ_{ijs}, depends on the shift structure in place at a facility as well as the facility. The reasoning behind this follows a recent review of capacity at Site 1A (Lehman 2010) which led to the identification of the following five primary shift structures to be evaluated in this model:

I. available at Site 1A (for each VI and SYR, all shifts are 5x24)
   1) 2 lines, shared run crew, no setup crew (2Lx1Rx0S)
   2) 2 lines, shared run crew + shared setup crew (2Lx1Rx1S)
   3) 2 lines, 2 dedicated run crews, no setup crew (2Lx2Rx0S)

II. available at Site 1B & RMS (for each VI and SYR all shifts are 5x24)
   4) 1 line, dedicated crew, no setup crew (1Lx1Rx0S)
   5) 1 line, dedicated crew, shared (1Lx1Rx1S)

Under options (2) and (5) above, a shared setup crew would be available to perform the line clear, sanitization and setup functions for two lines. In the case of Site 1A, there will be two shared setup crews, one with responsibility for two VI lines and one for two SYR lines. In the case of Site 1B and RMS, there will be a setup crew in each location responsible for one VI and one SYR line.

In either of these cases, the presence of the shared setup crew causes the setup to occur independent of the schedule of the run crew. Thus, from a time consumption perspective, the setup is free. By contrast, the other options require the run crew to perform the setup, and thus consume line capacity. For Site 1A, this is the case for both the single run crew option (1), and the two run crew option (3) where line hours available are doubled, but capacity is still consumed for each setup.

Thus, the table of time consumed for each lot setup, ξ_{ijs}, depends on shift structure as well as facility and product, whereas the table for line run times, ζ_{ij}, only depends on product and facility. The practical implications of this can be seen in Figure 16 below, where the tradeoffs between run time and changeover time are seen in light of different staffing scenarios. It is interesting to note that, at all points where changeovers are as long as average batch run times, having one line crew staffed per line type (i.e. one vial line run crew and one syringe line run crew, as shown in Figure 16.c), is as efficient as having four total crews (one each for the two vial lines and two syringe lines, as shown in Figure 9.d). These equivalence is also shown at the point of intersection on Figure 16.a.

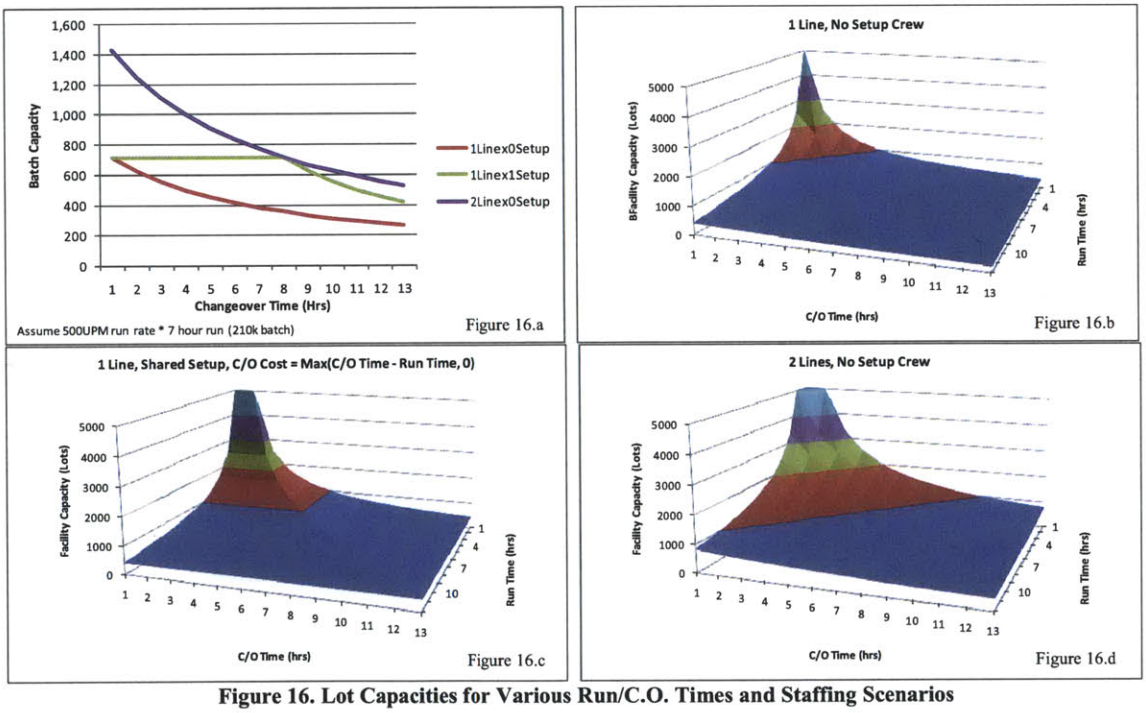

Figure 16. Lot Capacities for Various Run/C.O. Times and Staffing Scenarios

Appendix C. Example Variable Staffing Cost Calculation

Current fully-burdened salaries for four types of employees (Operations, Process Development, Quality and General Management) were provided for FY2010 by the finance group. As is shown below in Table 8, the true numbers have been obfuscated and a 2.5% per annum increase in these costs was assumed.

Average Wage + Benefits

Annual Wage Incr			2.50%			
Wage Rates			Average Wage + Benefits			
Site	Year	Site-Year	Ops	PD	Quality	General
Site-1A	2010	Site-1A-2010	$XX	$XXX	$XXX	$XXX
Site-1B	2010	Site-1B-2010	$XX	$XXX	$XXX	$XXX
RMS	2010	RMS-2010	$XX	$XXX	$XXX	$XXX
Site-1A	2013	Site-1A-2013	$XX	$XXX	$XXX	$XXX
Site-1B	2013	Site-1B-2013	$XX	$XXX	$XXX	$XXX
RMS	2013	RMS-2013	$XX	$XXX	$XXX	$XXX

Table 8. Estimated Headcount Costs for Future Years by Employee Type [OBFUSCATED]

Next a generic staffing plan, by function, employee type and staffing scenario, was created for each formulation and fill facility. An obfuscated example of such a plan is included as Table 9 below. A sum-product was performed on the relevant items in these two tables in order to determine the incremental cost to provide a given amount of capacity (line-hours) at any facility in any given year. This approach captures the step-function nature of these costs, which are variable in the long-run but fixed in the short-run from Amgen's perspective.

Headcount by Site

Indirect HC Factors	
PD	0.3
Quality	0.25
General	0.1

Site-ShiftStruct	Min. Crew	1-Line	1-Line + Setup	2-Line
Direct HC	**48**	**90**	**100**	**134**
SYR Formulation	2	3	3	6
VI Formulation	2	3	3	3
UF/DF	3	5	5	5
SYR Setup	0	-	5	-
SYR Fill	7	14	14	21
VI Setup	0	-	5	-
VI Fill	6	12	12	24
Flex Setup	0	-	-	-
Flex Fill	0	-	-	-
Inspect-SYR	5	10	10	10
Inspect-VI	3	5	5	5
Dispensing	2	3	3	6
Tank Wash	4	8	8	16
Transfer Point	3	5	5	10
Component Prep	3	6	6	12
Sanitors	8	16	16	16
Indirect HC	**31**	**59**	**65**	**87**
PD	14	27	30	40
Quality	12	23	25	34
General	5	9	10	13

Table 9. Generic Facility Headcount Plan by Function and Staffing Scenario [OBFUSCATED]

Appendix D. Data Model Description and Data Collection

a. Data Model: Table used by Optimization Model

The purpose of this section is to outline the skeleton of the data that is needed to populate the Model, without any reference to how it was collected or aggregated.

The necessary data for the optimization model flows rather naturally from the description of the constraints and objective function above (as these require input data whereas the output from the decision variables will come out of the model). The tables of data that will be needed to properly run the model are as follows:

Index tables: to properly define the dimension of all indices:

- ***i***: the list of all products, identified by a unique key (i.e. DP SKU)
- ***j***: the list of all fill facilities, identified by a unique key such as "Site 1A"
- ***l***: the list of all distribution centers, identified by a unique key such as "LDC"
- ***n***: the list of years to be analyzed in the model such as [2013 … 2017]
- ***s***: the list of shift structures available, identified by a unique key such as "5x24x1Rx0S"[8]

Input data tables:

- ***qry_ie***:
  1. purpose: to provide all of the necessary inputs that vary with combinations of products ***i*** and lots ***e***
  2. key columns: [***i***, ***e***]
  3. data items (additional columns): [lot size tagline, lot size (in units)]
  4. number of rows = (length of ***i***)*(length of ***e***)
- ***qry_iln***
  1. purpose: to provide all of the necessary inputs that vary with combinations of products ***i***, distribution centers ***l***, and years ***n***
  2. key columns: [***i***, ***l***, ***n***]
  3. data items (additional columns): [Demand, RMS tax per unit, Site 1A tax per unit, DS source is Site 1A (yes/no)]
  4. number of rows = (length of ***i***)*(length of ***l***)* (length of ***n***)
- ***qry_jsn***
  1. purpose: to provide all of the necessary inputs that vary with combinations of facilities ***j***, shift structures ***s***, and years ***n***
  2. key columns: [***j***, ***s***, ***n***]

[8] This nomenclature means 5 hours/week by 24 hours/day by 1 run crew/line by 0 shared setup crews/every two lines

3. data items (additional columns): [cost of implementing shift structure, bottleneck line hours provided]
4. number of rows = (length of ***j***)*(length of ***s***)* (length of ***n***)

- ***qry_ij***
  1. purpose: to provide all of the necessary inputs that vary with combinations of products ***i*** and fill facilities ***j***
  2. key columns: [***i, j***]
  3. data items (additional columns): [lot run speed, cost of setup, variable component of inventory value through fill process, "***tau***"]
  4. number of rows = (length of ***i***)*(length of ***j***)
- ***qry_ijse***
  1. purpose: to provide all of the necessary inputs that vary with combinations of products ***i***, facilities ***j***, shift structures ***s***, and lot sizes ***e***
  2. key columns: [***i, j, s, e***]
  3. data items (additional columns): [lot setup time]
  4. number of rows = (length of ***i***)*(length of ***j***)* (length of ***s***)* (length of ***e***)
- ***qry_ijl***
  1. purpose: to provide all of the necessary inputs that vary with combinations of products ***i***, facilities ***j***, and distribution centers ***l***
  2. key columns: [***i, j, l***]
  3. data items (additional columns): [variable component of inventory value on hand at distribution center, "***b***"]
  4. number of rows = (length of ***i***)*(length of ***j***)* (length of ***l***)
- ***qry_i_ICO***
  1. purpose: to provide all of the necessary inputs that vary with products ***i*** in the ICO markets
  2. key columns: [***i***]
  3. data items (additional columns): [minimum production frequency for ICO market]
  4. number of rows = (length of ***i***)
- ***qry_ijn_SSk***
  1. purpose: to hold *SS* matrix described in Section 4.5
  2. key columns: [***i, j, n***]
  3. data items (additional columns): [assumed minimum production level (in units) of product *i* at facility *j* in year *n*, raised to the power of 0.2]
  4. number of rows = (length of ***i***)*(length of ***j***)* (length of ***n***)

b. Data Preparation in Excel and Access

The purpose of this section is now to outline the tools and methods that were used to collect and prepare the data for the Model.

- ***qry_ie***:

1. a list of all of the validated batch ranges were collected from the appropriate Corporate planners (for source data see [Project Root Folder]\Data_Collection\Validated_Batch_Ranges)
2. these were consolidated into a single list, given a tagline from 1-8 based on a batch sizes estimated relative position on a total scale of potential batch sizes (very rough estimate), and then with the DP SKU and tagline as key columns, entered in the Model Database as table "ie"

- ***qry_iln***
  1. Cognos demand was pulled and imported into Model Database as "LE_C_2009"
  2. Rapid Response Multi-Level BOM data was pulled to make a best-effort match of all FDP SKUs to DP SKUs (missing links between the two resolved by asking Commercial Product managers). The result of this process is the Model Database table "FDP_DP_matchFiltered_mTbl1." It is important to note that perfection was not the goal of this match and often times a DP SKU was tied to an FDP SKU without caring about a DP SKU suffix (e.g. 01831B, 01831C, and 01831D are all fundamentally the same filled DP, comprised of the same formulated d-mab – the only difference is the source of the DS, which is not relevant to this analysis as we are assuming a single predominant DS source for purposes of determining the transportation cost to the fill site)
  3. "LE_C_2009" and "FDP_DP_matchFiltered_mTbl1" are combined and aggregated thought a number of queries in the Model Database to result in qry_iln.
- ***qry_jsn***
  1. A model for capacity options and costs was developed in Excel ([Project Root Folder]/Data_Collection/Capacity/jsn_Model.xlsx)
  2. In this model, 2010 labor and benefits figures for Ops / PD and Quality employees at Site 1A and Site 2 (proxy for RMS) were provided by David Yapp, and 2.5% annual increase was assumed.
  3. Exact staffing counts by shift structure were estimated and are shown on the sheet pi_Calc.
  4. For bottleneck capacity, the average of (Effective Production Time + Actual Changeovers) by year was collected from Peter Pick's recent capacity analysis. This was assumed to be the capacity of a single line, whereas two lines were assumed to by twice this number and low-burn was assumed to by ½.
  5. Cost and bottleneck hours available are aggregated on the worksheet jsn_calc of the Excel book – fields from this sheet were then populated directly into the Model Database.
- ***qry_ij***
  1. The following supporting external data tables were collected and entered into the Model Database
     a. xData_BulkCost_perAG (source: Rapid Response Inventory Valuation)
     b. xData_WAvg_Actual_Cost_by_DP (source: Rapid Response Inventory Valuation))
     c. xData_TransportLanes_Costs (source: Gary Hutchinson, see [Project Folder]\Data_Collection\Transportation)

d. xData_UnitSpaceReqs_FINAL (source: Bill Keefe warehousing analysis with minor additions for missing SKUs based on most similar completed SKU – see [Project Folder]\Data_Collection\Unit_Space_req)
e. xData_Consolidated_Run_Setup_new (see [Project Source]\Data_Collection\Capacity\Consolidated_Run_Setup.xlsx)
    i. Current run times were collected from Peter Pick's recent capacity work at Site 1A and entered into the sheet x_Data_Consolidated_Run_Setup, and then uploaded into the table xData_Consolidated_Run_Setup_new
    ii. Site 1B was assumed to have 500UPM for SYR and 600UPM for VI. RMS is assumed to have a factor of the above for all run speeds, as specified in the Universal_Variables table

2. The above external data was combined in the Model Database to yield lot run speeds, costs of setups and variable cost of inventory for all product and facility combinations.

- ***qry_ijse***

1. The following supporting external data table was collected and entered into the Model Database
    a. xData_Consolidated_Run_Setup_new (see [Project Source]\Data_Collection\Capacity\Consolidated_Run_Setup.xlsx)
        i. Current Changeover times were collected from Peter Pick's recent capacity work and entered into sheet xData_Site 1A_js_CO_time, and then uploaded to the table of the same name in the Model Database
        ii. Change-over factors were entered into the table "j" of the Model Database for all fill facilities, based on a factor of the above Site 1A data
2. Within the model database, lot setup times are calculated based on the business rule that they should be equal to the factored change over time in the event of no shared crew, or the greater of zero or difference in the change over time and the run time in the event of a shared crew. These can be shown to be the amount of bottleneck line time that would be consumed by changeover operations.

- ***qry_ijl***

1. This follows the same logic and data sources as qry_ij, and simply appends the value of the second transportation leg between the fill site and the distribution center.

- ***qry_i_ICO***

1. Minimum production frequencies, as developed in Section 4, should be added to the table "i" of the Model Database

- ***qry_ijn_SSk***

1. Data was extracted from *qry_ie* to provide minimum feasible batch sizes by product. This set was then expanded (multiplied) by all facilities *j* and years *n*. This base set of data was then joined with a table of input data (holding 1st iteration x^* values) and the maximum, by *i, j* and *n* was taken as the final value.

Appendix E. Amgen Inc. Geographic Footprint: Facilities and Capabilities

Location	Number of spaces or buildings: Owned	Number of spaces or buildings: Leased	Manufacturing: Commercial: Aranesp®	Neulasta®	NEUPOGEN®	Epoetin alfa	Enbrel®	Other Products	Clinical: denosumab	Clinical: Other	Other Functions: Administrative	Research and/or Development	Sales and Marketing	Warehouse	Distribution Center
United States:															
Thousand Oaks, California	36	6							F	B F	✔	✔	✔	✔	✔
Fremont, California	-	4						B F		B	✔			✔	
San Francisco, California	-	5									✔	✔			
Boulder, Colorado	2	2						B	B	B	✔			✔	
Longmont, Colorado	6	1				B				B	✔			✔	
Washington, D.C.	-	1									✔		✔		
Louisville, Kentucky	1	-												✔	✔
Cambridge, Massachusetts	1	-										✔			
Foxboro, Massachusetts	-	1												✔	
West Greenwich, Rhode Island	6	-					B			B	✔			✔	
Bothell, Washington	3	1										✔		✔	
Seattle, Washington	6	1									✔	✔			
Other U.S. cities	-	6									✔		✔		
Outside United States:															
Canada	-	3									✔	✔	✔		
Puerto Rico	19	-	B F	B F	B F	F	F	F	F	B F	✔			✔	
Australia	-	5									✔		✔		
Japan	-	1									✔	✔			
Netherlands	8	1	F1	F1	F1			F1	F1	F1	✔		✔	✔	✔
Ireland	-	2									✔		✔		
Switzerland	-	2									✔		✔		
United Kingdom	-	4									✔	✔	✔		
Other countries	-	35										✔	✔		

B - Bulk manufacturing
F - Formulation, Fill and Finish
F1 - Finish only

Source: Amgen Inc. 2009 Annual Report, p.57

Appendix F. CPLEX Implementation

```
/*********************************************
 * OPL 12.2 Model
 * Author: rlehman
 * Creation Date: Sep 1, 2010 at 9:00:25 AM
 *********************************************/

 //Indices

tuple Product_to_Family
{
  string DP_SKU;
  string Family;
}

{Product_to_Family} Product = ...;      //    i           Products
{string} Family = ...;                  //    m           Product family
{string} FillF = ...;                   //    j           Fill facilities
{string} DistC = ...;                   //    l           Distribution centers

tuple Product_LotScenario
{
 string DP_SKU;
 string Family;
 string LotScenario;
 int f;
}
{Product_LotScenario} Product_Lot = ...;      //    e           Lot Scenario
{string} ShiftStruct = ...;
//    s           Shift structure (e.g. 5x24xLowBurn, 5x24x1, 5x24x2 7x24x2)
{int} Year = ...;                             //    n           Year of analysis
float WACC = 0.1;
//    WACC  Amgen's weighted average cost of capital assumed in model (10%)
float LIMIT = 0.5;
//    LIMIT  Limit on amount of global production (overall or by product) that can be
produced at RMS. Set to 0.5 as a default. Set to 1.0 for no limitation.
//Tuple definitions for outputs files
tuple Fill_Lot_Allocation {
      //    x           Cost minimizing product allocation (lots allocated)
  string DP_SKU;
  string LotScenario;
  string FillF;
  string ShiftStruct;
  string DistC;
  int Year;
  int Value;
}
tuple Fill_ShiftStructures {
      //    psi         boolean, FillF adopts ShiftStruct s
  string FillF;
  string ShiftStruct;
  int Year;
  int Value;
  float Staff_Costs;
}
tuple Fill_Utilization {
  string FillF;
  int Year;
  float Hours_Consumed;
  float Hours_Available;
```

```
}

tuple Fill_Units_to_Market {
  string Product;
  string DistC;
  int Year;
  float Units_to_Market;
  float D;
}

tuple Fill_EU_Prod_by_Fam {
  string Family;
  int Year;
  float EU_Prod_by_Fam;
  float Global_D_by_Fam;
}

tuple Fill_Cost_Detail {
  string Product;
  string FillF;
  string ShiftStruct;
  string DistC;
  string Lot_Scenario;
  int Year;
  int x;
  float eta;
  float Setup_Costs;
  int f;
  int Units;
  float b;
  float Unit_Var_Costs_by_e;
  float RMS_Tax_Costs;
  float Site 1A_Tax_Costs;
  float c;
  float Safety_Stock_Costs;
}

tuple Fill_Cycle_Inv_Costs {
  string Product;
  string FillF;
  string Lot_Scenario;
  int Year;
  float tau;
  float WACC;
  float Cycle_Inv_Costs;
}

//Input data definition
      //by Product, Distribution Center and Year

float D[Product, DistC, Year] = ...;
             //     D            Demand for Product i by DistC l and Year n
float RMS_Tax[Product, DistC, Year] = ...;
             //     RMS_tax      Calculated in MS_Access, tax to be paid on profits of
             products flowing through RMS
float Site 1A_Tax[Product, DistC, Year] = ...;
             //     Site 1A_tax  Calculated in MS_Access, tax to be paid on revenues
             of products flowing through Site 1A
int DS_Source_Site 1A[Product, DistC, Year] = ...;
             //                  Indicator for wheter or not bulk manufacturing occurs
             in Site 1A (for purposes of calculating Site 1A tax burden)
```

```
      //by Fill Facility, Shift Structure and Year
float pi[FillF, ShiftStruct, Year] = ...;
            //    pi          cost of staffing FillF j with form/fill ShiftStruct s
            in Year n
int phi[FillF, ShiftStruct, Year] = ...;
            //    phi         annual form/fill capacity (in line-hrs) at FillF j
            given ShiftStruct s in Year n


      //by Product and Fill Facility
float eta[Product, FillF] = ...;
            //    eta         variable lot setup costs (non-HC, e.g. yield loss in
            tank) for each fill lot as FillF j
float xi[Product_Lot, FillF, ShiftStruct] = ...;
            //    xi          lot form/fill setup time (hrs) for Product i at FillF
            j
int zeta[Product, FillF] = ...;
             //   zeta   form/fill line run speed for Product i at FillF joat
            tau[Product, FillF] = ...;
            //  tau           sum of upstream, per unit replacement costs (variable
            only) were a unit to be scrapped in filling stage
float tau[Product, FillF] = ...;
            //  tau           sum of upstream, per unit replacement costs (variable
            only) were a unit to be scrapped in filling stage
float c[Product, FillF] = ...;
            //    c           per-unit safety stock holding cost for product i at
            facilty j
int SSk[Product, FillF, Year] = ...;
            //  SSk           assumed sqrt(Demand) by product i and facility
            k, for purposes of calculating safety stock

      //by Product, between Fill Facility and Distribution Center
float b[Product, FillF, DistC] = ...;
            //    b           sum of per-unit comprehensive variable to FF Product
            i at FillF j and ship to DistC L (costs associated with raw materials,
            transportation (upstream & downstream) and tax)


      //by Product (for ICO Distribution Center)
int alpha[Product] = ...;
            //    alpha  min production frequency of Product i given constraints of
            markets within ICO footprint [lots/year]


//Variable definition

dvar int+ x[Product_Lot][FillF][ShiftStruct][DistC][Year];  //    x           Lots
of Product i filled at FillF j and sent to DistC l in Year n

dvar boolean psi[FillF][ShiftStruct][Year];                 //    psi
      Boolean for whether or not shift structure s is scheduled at FillF j in Year n

dvar boolean f_b[Product_Lot, FillF, Year];   //    f_b         Boolean for whether
or not lot size e is selected for product  at facility j in year n

//ILOG CPLEX settings

execute PARAMS {
  cplex.tilim = 1800;
}
execute SETTINGS {
  settings.displayComponentName = true;
```

```
  settings.displayWidth = 40;
}


//Objective function definition

minimize
 sum( i_e in Product_Lot, j in FillF, s in ShiftStruct, l in DistC, n in Year )
((i_e.f*x[i_e][j][s][l][n]) * b[<i_e.DP_SKU,i_e.Family>,j,l]) +  //variable (linear)
unit costs, except tax

 sum( i_e in Product_Lot, j in FillF:j=="RMS", s in ShiftStruct, l in DistC, n in Year
) ((i_e.f*x[i_e][j][s][l][n]) * RMS_Tax[<i_e.DP_SKU,i_e.Family>,l,n]) +
//variable (linear, per unit) taxes on Profits flowing through RMS

 sum( i_e in Product_Lot, j in FillF:j=="Site 1A", s in ShiftStruct, l in DistC, n in
Year ) ((i_e.f*x[i_e][j][s][l][n]) * Site 1A_Tax[<i_e.DP_SKU,i_e.Family>,l,n] *
DS_Source_Site 1A[<i_e.DP_SKU,i_e.Family>, l, n]) +
//variable (linear, per unit) taxes on Revenues flowing through Site 1A (Site 1A)

 sum( i_e in Product_Lot, j in FillF:j=="Site 1B", s in ShiftStruct, l in DistC, n in
Year ) ((i_e.f*x[i_e][j][s][l][n]) * Site 1A_Tax[<i_e.DP_SKU,i_e.Family>,l,n] *
DS_Source_Site 1A[<i_e.DP_SKU,i_e.Family>, l, n]) +
//variable (linear, per unit) taxes on Revenues flowing through Site 1A (Site 1B)

 sum( i_e in Product_Lot, j in FillF, s in ShiftStruct, l in DistC, n in Year )
(x[i_e][j][s][l][n] * eta[<i_e.DP_SKU,i_e.Family>,j]) +
//variable (linear) lot costs

 sum( j in FillF, s in ShiftStruct, n in Year ) (psi[j][s][n] * pi[j,s,n]) +
//staffing costs

 sum( i_e in Product_Lot, j in FillF, n in Year ) (f_b[i_e][j][n] * i_e.f *
tau[<i_e.DP_SKU,i_e.Family>][j] * WACC) / (2) +
//cycle inventory holding costs

sum( i_e in Product_Lot, j in FillF, s in ShiftStruct, n in Year)
(c[<i_e.DP_SKU,i_e.Family>][j] * (sum (l in DistC) (i_e.f*x[i_e][j][s][l][n]) /
SSk[<i_e.DP_SKU,i_e.Family>][j][n]);
//safety stock inventory holding costs

//Constraint definition
subject to {

  forall( i in Product, l in DistC, n in Year )
    DistC_Demand:
            //      sum( j in FillF ) (_X[i][j][l][n]) >= D[i,l,n];
       sum( j in FillF, i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU, s in ShiftStruct )
(i_e.f*x[i_e][j][s][l][n]) >= D[i,l,n];
//     Units_to_Market[i][l][n] >= D[i,l,n];

  forall( j in FillF, n in Year)
    Fill_Capacity:
            //      (sum( i in Product, e in LotScenario, l in DistC)
((x[i][j][l][e][n]*xi[i,j]) + (_X[i][j][l][n]/(60*zeta[i,j])))) -
       (sum( i_e in Product_Lot, l in DistC, s in ShiftStruct)
((x[i_e][j][s][l][n]*xi[i_e,j,s]) +
((i_e.f*x[i_e][j][s][l][n])/(60*zeta[<i_e.DP_SKU,i_e.Family>,j])))) -
       (sum(s in ShiftStruct) (psi[j][s][n]*phi[j,s,n])) <= 0;
//     Hours_Consumed[j][n] <= Hours_Available[j][n];

  forall (j in FillF, n in Year)
    Single_Shift_Stucture:
```

```
      sum( s in ShiftStruct ) psi[j][s][n] <= 1;

  forall (i in Product, j in FillF, n in Year)
    Single_Lot_Size_Selected:
      sum( i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU ) f_b[i_e][j][n] <= 1;

  forall (i_e in Product_Lot, j in FillF, n in Year)
    Within_Selected_Lot_Size:
      sum( s in ShiftStruct, l in DistC ) x[i_e][j][s][l][n] <=
f_b[i_e][j][n]*999999999;

  forall (i_e in Product_Lot, j in FillF, s in ShiftStruct, n in Year)
    Within_Selected_Shift_Structure:
      sum( l in DistC ) x[i_e][j][s][l][n] <= psi[j][s][n]*999999999;

// In following section,
// turn on Non_EU_Min_Production and turn off EU_Max_Production,
// or vice versa for different scenarios
//
  forall ( i in Product, n in Year:n>=2014)
    EU_Min_Production:
      sum( s in ShiftStruct, l in DistC, i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU)
(x[i_e]["RMS"][s][l][n]*999999999) - sum(l in DistC) (D[i][l][n]) >= 0;

 // forall ( i in Product, n in Year)
 //   Non_EU_Min_Production:
 //     sum( s in ShiftStruct, l in DistC, i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU)
((x[i_e]["Site 1A"][s][l][n]+x[i_e]["Site 1B"][s][l][n])*999999999) >= sum(l in DistC)
D[i][l][n];

// End of section for EU_Min_Production / Non_EU_Min_Production switch

// In following section,
// turn on EU_Max_Production and turn off EU_Max_Production_by_Family,
// or vice versa for different scenarios
//
  forall (n in Year)
    EU_Max_Production:
            sum( i_e in Product_Lot, l in DistC, s in ShiftStruct )
(i_e.f*x[i_e]["RMS"][s][l][n]) <= LIMIT * sum(i in Product, l in DistC) (D[i][l][n]);

// forall (m in Family, n in Year)
 //   EU_Max_Production_by_Family:
 //   sum( i_e in Product_Lot: i_e.Family == m, l in DistC, s in ShiftStruct )
(i_e.f*x[i_e]["RMS"][s][l][n]) <= LIMIT * sum(i in Product: i.Family == m, l in DistC)
(D[i][l][n]);
//     EU_Prod_by_Fam[m][n] <= LIMIT * Global_D_by_Fam[m][n];

//
// End of section for EU_Max_Production / EU_Max_Production_by_Family switch

  forall (i in Product, n in Year)
    Min_Production_Frequency:
      sum(j in FillF, s in ShiftStruct, i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU)
x[i_e][j][s]["Site 2"][n] >= alpha[i];

}

//Output

{Fill_Lot_Allocation} out_Fill_Lot_Allocation =
{<i_e.DP_SKU,j,s,l,i_e.LotScenario,n,(x[i_e][j][s][l][n])>
```

```
      |i_e in Product_Lot, j in FillF, s in ShiftStruct, l in DistC, n in
Year:x[i_e][j][s][l][n]>0};

{Fill_ShiftStructures} out_Fill_ShiftStructures = {<j,s,n,psi[j][s][n],(psi[j][s][n] *
pi[j,s,n])>
      |j in FillF, s in ShiftStruct, n in Year:psi[j][s][n]>0};

{Fill_Utilization} out_Fill_Utilization = {<j,n,sum( i_e in Product_Lot, l in DistC, s
in ShiftStruct) ((x[i_e][j][s][l][n]*xi[i_e,j,s]*psi[j][s][n]) +
((i_e.f*x[i_e][j][s][l][n])/(60*zeta[<i_e.DP_SKU,i_e.Family>,j]))),sum(s in
ShiftStruct) (psi[j][s][n]*phi[j,s,n])>
      |j in FillF, n in Year};

{Fill_Units_to_Market} out_Fill_Units_to_Market = {<i.DP_SKU,l,n,sum( j in FillF, s in
ShiftStruct, i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU
)(i_e.f*x[i_e][j][s][l][n]),D[i,l,n]>
      |i in Product, l in DistC, n in Year};

{Fill_EU_Prod_by_Fam} out_Fill_EU_Prod_by_Fam = {<m,n,sum( i in Product: i.Family ==
m, s in ShiftStruct, l in DistC) ( sum( i_e in Product_Lot:i_e.DP_SKU == i.DP_SKU )
(i_e.f*x[i_e]["RMS"][s][l][n])),sum(i in Product: i.Family == m, l in DistC)
(D[i][l][n])>
      |m in Family, n in Year};

{Fill_Cost_Detail} out_Fill_Cost_Detail = {<i_e.DP_SKU, j, s, l, i_e.LotScenario, n,
x[i_e][j][s][l][n],eta[<i_e.DP_SKU,i_e.Family>][j], (x[i_e][j][s][l][n] *
eta[<i_e.DP_SKU,i_e.Family>,j]),i_e.f,
i_e.f*x[i_e][j][s][l][n],b[<i_e.DP_SKU,i_e.Family>][j][l],
(i_e.f*x[i_e][j][s][l][n]*b[<i_e.DP_SKU,i_e.Family>,j,l]),
i_e.f*x[i_e][j][s][l][n]*RMS_Tax[<i_e.DP_SKU,i_e.Family>,l,n]*(j=="RMS"),
i_e.f*x[i_e][j][s][l][n]*Site 1A_Tax[<i_e.DP_SKU,i_e.Family>,l,n]*DS_Source_Site
1A[<i_e.DP_SKU,i_e.Family>,l,n]*((j=="Site 1A")+(j=="Site
1B")),c[<i_e.DP_SKU,i_e.Family>][j],
(c[<i_e.DP_SKU,i_e.Family>][j]*(i_e.f*x[i_e][j][s][l][n])/(SSk[<i_e.DP_SKU,i_e.Fami
ly>][j][n]))>
|i_e in Product_Lot, j in FillF, s in ShiftStruct, l in DistC, n in
Year:x[i_e][j][s][l][n]>0};

{Fill_Cycle_Inv_Costs} out_Fill_Cycle_Inv_Costs = {<i_e.DP_SKU, j, i_e.LotScenario, n,
tau[<i_e.DP_SKU,i_e.Family>][j], WACC, ((f_b[i_e][j][n] * i_e.f *
tau[<i_e.DP_SKU,i_e.Family>][j] * WACC) / (2))>
      |i_e in Product_Lot, j in FillF, n in Year:((f_b[i_e][j][n] * i_e.f *
tau[<i_e.DP_SKU,i_e.Family>][j] * WACC) / (2))>0};
```

```
/*********************************************
 * OPL 12.2 Data
 * Author: rlehman
 * Creation Date: Sep 1, 2010 at 9:00:26 AM
 *********************************************/

//SheetConnection sheet("AMGN_FF_Opt_v4.xlsx");
  SheetConnection output("output/output_00_NEXT.xlsm");
  DBConnection db("access","db4_a.accdb");

//Indices
       Product from DBRead(db,"SELECT i, DS_SKU FROM qry_i");
       Family from DBRead(db,"SELECT DS_SKU FROM qry_m");
       FillF from DBRead(db, "SELECT j from j");
       DistC from DBRead(db, "SELECT l from l");
       Year from DBRead(db,"SELECT n from n");
       ShiftStruct from DBRead(db, "SELECT s from qry_s");

//Input data
 //by Product
       Product_Lot from DBRead(db,"SELECT i,DS_SKU,e,f from qry_ie_Pos");
 //by Product, DistC and Year
       D from DBRead(db,"SELECT q_i,q_DS_SKU,q_l,q_n,D_int FROM qry_iln");
       RMS_Tax from DBRead(db,"SELECT q_i,q_DS_SKU,q_l,q_n,RMS_Tax FROM qry_iln");
       Site 1A_Tax from DBRead(db,"SELECT q_i,q_DS_SKU,q_l,q_n,Site 1A_Tax FROM
qry_iln");
       DS_Source_Site 1A from DBRead(db,"SELECT q_i,q_DS_SKU,q_l,q_n,iSrc_is_Site 1A
FROM qry_iln");
 //by FillF, Shift Structure and Year
       pi from DBRead(db,"SELECT j,s,n,pi FROM qry_jsn");
       phi from DBRead(db,"SELECT j,s,n,phi_Calc FROM qry_jsn");
 //by Product and FillF
       eta from DBRead(db,"SELECT ij.i,DS_SKU,j,eta FROM qry_ij");
       xi from DBRead(db,"SELECT qry_ijs.i,qry_ijs.DS_SKU,e,f,qry_ijs.j,s,xi FROM
qry_ijse");
       zeta from DBRead(db,"SELECT ij.i,DS_SKU,j,zeta FROM qry_ij");
       tau from DBRead(db, "SELECT i,DS_SKU,j,tau from qry_ij");
       c from DBRead(db,"SELECT i,DS_SKU,j,c FROM qry_ij"); //Calc'd from tau
       SSk from DBRead(db,"SELECT i, DS_SKU, j, n, SSk FROM qry_ijn_SSk");
//by Product, FillF and DistC
       b from DBRead(db,"SELECT ijl.i,DS_SKU,ijl.j,l,b FROM qry_ijl");
//by Product (for ICO DistC)
       alpha from DBRead(db, "SELECT i,DS_SKU,alpha_int FROM qry_i_ICO");

//Output
//Write fill Shift structures and lot allocations
out_Fill_Lot_Allocation to SheetWrite(output,"sol_Fill_Alloc!A2:G9001");
out_Fill_ShiftStructures to SheetWrite(output,"sol_Fill_Shifts!A2:E9001");
out_Fill_Utilization to SheetWrite(output,"sol_Fill_Util!A2:D9001");
out_Fill_Units_to_Market to SheetWrite(output,"sol_Fill_Units!A2:E9001");
out_Fill_EU_Prod_by_Fam to SheetWrite(output,"sol_Fill_EU_Prod!A2:D9001");
out_Fill_Cost_Detail to SheetWrite(output,"sol_Fill_Cost_Detail!A2:Q9001");
out_Fill_Cycle_Inv_Costs to SheetWrite(output,"sol_Fill_Cycle_Inv_Costs!A2:G9001");
```