# An Analysis and Mitigation of Demand Variability on External Supply Chains

by

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

**Master of Science in Mechanical Engineering**
**and**
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## ABSTRACT

In the pharmaceutical industry, increasing product complexity, shifts towards specialty medicine and growth in emerging markets have resulted in increased forecast variation and manufacturing complexity for new products. In the past six years, AstraZeneca has outperformed its peers in research and development productivity, increasing the number and speed of product launches. The resulting demand variability and shifting operational environment have led to financial and non-financial impacts, such as poor inventory performance and strained supplier relationships. The objective of this research is to identify processes and procedures that amplify the impact of demand variability and the areas in the end-to-end operation that are significantly impacted. The secondary objective is to identify process improvements in the existing system and develop strategies to mitigate the risk of demand variability.

This thesis presents an analysis of the impact of demand variability on the external manufacturing and supply chain operations for new products. A case study approach is used to assess its impact on the forecast processes, manufacturing systems and supplier relationships. A simulation tool was developed as a method to measure financial impact based on inventory performance. The simulation was expanded for use as a decision assist tool to evaluate test cases developed from the current state analysis.

The research illustrates that the end-to-end manufacturing and supply chain operation is experiencing significant bullwhip effects for new products. The primary sources of financial impacts are the policy stock requirements tied to monthly demand and segmentation of the supply chain causing different forecasts to be used for certain stages. Non-financial impacts include loss of trust with suppliers, manually managed complexity and limited communication resulting in the bullwhip effect. The short-term and long-term recommendations focus on increased operational transparency and scenario-based forecast planning to mitigate the impact of demand variability on the system. Pilot programs for statistical process control implementation in drug substance manufacturing and development of a future state commercial partnership model were defined as follow-up work to this research

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## Acronyms

| | |
|---|---|
| Active Pharmaceutical Ingredient | API |
| AstraZeneca | AZ |
| Contract Manufacturing Organization | CMO |
| Food and Drug Administration | FDA |
| Global External Sourcing | GES |
| Global Portfolio & Product Strategy | GPPS |
| Leaders for Global Operations | LGO |
| Massachusetts Institute of Technology | MIT |
| New Molecular Entity | NME |
| New Product Introduction | NPI |
| Operations Senior Leadership Team | OSLT |
| Research and Development | R&D |
| System Dynamics | SD |

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# 1 Introduction

The research and activities discussed in this thesis were performed from June to December 2018 as part of the Leaders for Global Operations (LGO) program at the Massachusetts Institute of Technology (MIT). The research was conducted as collaboration between AstraZeneca and MIT. It was hosted by AstraZeneca's Global External Sourcing (GES) organization out of the Macclesfield, UK site. This section outlines the relevant company information and industry analysis as background and project motivation. It then introduces the problem statement and research objectives guiding this work.

## 1.1 Company Information

AstraZeneca (AZ) is a leading, global biopharmaceutical company whose innovative medicines are used by millions of patients across over 100 countries. Headquartered in the UK, the company focuses on the discovery, development and commercialization of prescription medicines in three main therapy areas; oncology, cardiovascular & metabolic disease and respiratory disease. Their product portfolio is primarily small-molecule treatments but since the acquisition of MedImmune in 2006, the biologics business is expanding. Over the past six years, the company has successfully launched several new products and rebuilt their research & development (R&D) pipeline, making it one of the most productive pharmaceutical R&D organizations in the industry.

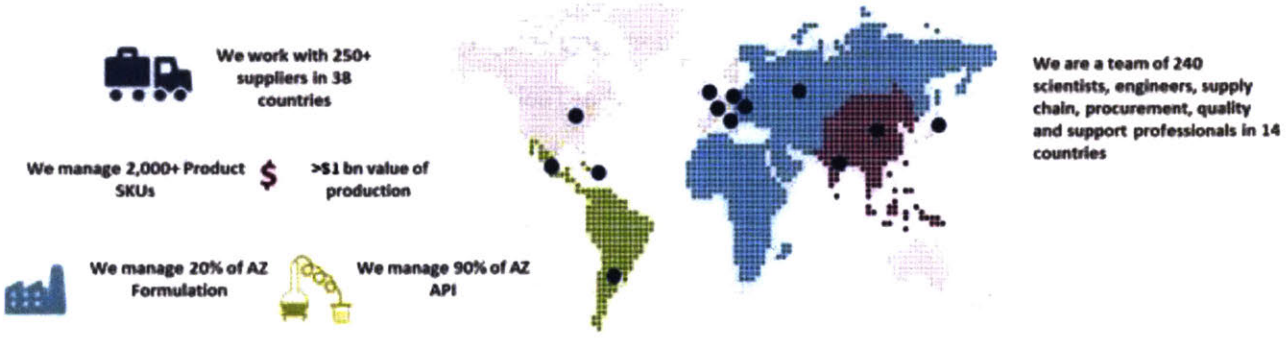


*Figure 1 - Global External Sourcing Organization Overview*

Global External Sourcing (GES) is the organization responsible for the development, maintenance and optimization of supply chains providing devices, active pharmaceutical ingredients (API), formulation/packaging and several other critical materials and services to AstraZeneca's small molecule business. An overview of the GES operation is shown in Figure 1.

The organization is responsible for the supply chain activities over a product's lifecycle as well as business development activities, including acquisition and divestments of products. As part of Global Operations within AstraZeneca, GES acts as a "virtual" supplier into the AstraZeneca internal manufacturing network and provides greater than $1 B in production value to the company annually.

In addition to the external manufacturing suppliers, GES works with the commercial marketing, Global Supply Chain & Strategy (GSC&S), Global Portfolio & Product Strategy (GPPS) and Pharmaceutical Technology & Development (PT&D) organizations within AstraZeneca to execute new supply chain strategies, launch products and support lifecycle management programs. These organizations in many cases are suppliers to GES of information and processes required for external manufacturing operations.

## 1.2 Current Environment and Motivation

Shifts in the health care industry and changing corporate strategies at AstraZeneca have generated a period of immense change for the company and the supply base over the past decade. The current state system and processes were not designed to optimally handle many of these changes such as the increased number of product launches, focus on specialty medicine and increased importance of emerging markets. This has resulted in significant deviations from inventory design volumes and an external manufacturing system incapable or sluggish to react to changing demand forecasts. Tension is created between the supply chain performance and AstraZeneca's return-to-growth and science led strategies by tying up cash in inventory. These funds could otherwise be used for R&D activities that fuel the company's future growth. Throughout 2018, there was intense focus on reducing unplanned inventory levels to free up cash flow for growth activities.

GES utilizes long-term demand forecasts for strategic capacity planning and executing supply contracts. Accurate demand forecasting is challenging, especially in the pharmaceutical industry where clinical trials and the regulatory environment are sources of major uncertainty. Long lead times and manufacturing offsets require API volume commitments on average three years prior to the demand consumption for the final product. A standard small-molecule pharmaceutical manufacturing system is divided in to drug substance and drug product manufacturing. At AstraZeneca, the drug substance manufacturing process operates on a push

system due to long lead times and drug product manufacturing is a pull system. The general process is shown in Figure 2.

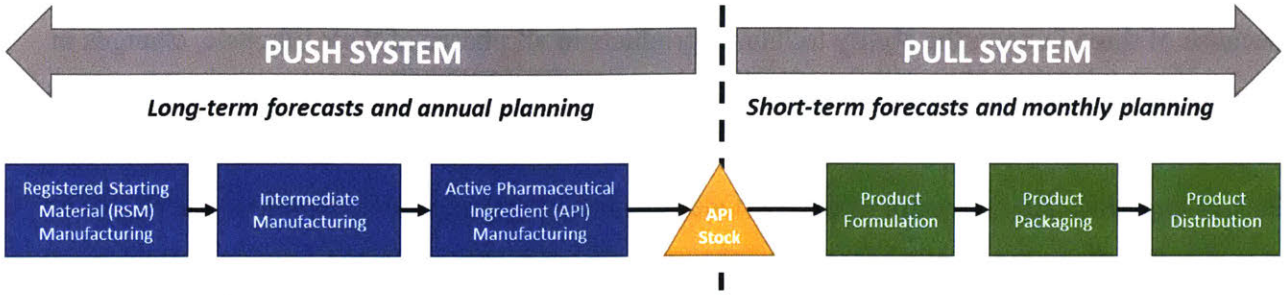


*Figure 2 - General Small Molecule Pharmaceutical Manufacturing Process Overview*

Forecasting is the responsibility of the commercial organization and forecast accuracy is critical to the performance of the external supply chains. Long-term forecast variability can lead to product shortage on one extreme and product waste on the other. This results in financial and non-financial impacts such as inventory write-offs, stockouts, sub-optimal supply contracts and damage to supplier relationships. The apparent increase in demand variability over the past few years has exacerbated these impacts.

Growth in emerging markets, changing regulatory frameworks, accelerated R&D, and advances in treatment and manufacturing technologies all contribute to shifting strategies at the brand, company and industry level. This research helps AstraZeneca understand how its end-to-end manufacturing and supply chain operation is reacting to these trends, identify areas or processes that magnify the impact of the this demand variability and propose a set of recommendations to mitigate the risks. This is a critical business need that supplements internal studies to define what it means to be a world class pharmaceutical supply chain and organization by 2025.

### 1.2.1 Expanding Pharmaceutical Industry

The growth of emerging markets is an exciting challenge for pharmaceutical companies as more patients across the globe gain access to life-saving medical treatments. The *Financial Times* defines an emerging market as one in a developing nation where there is a potential for high income with investment, but with high risk [26]. AstraZeneca's estimated 2018 financial results indicate that emerging markets are $1/3^{rd}$ of global sales, up from 18% in 2012 [6]. The

industry expects this trend to continue with growth in emerging markets outpacing growth in developed nations.

These markets are attractive to major pharmaceutical companies as growth opportunities because of three factors; the ability to launch products in all phases of their lifecycle, changes in disease patterns and low-cost manufacturing operations. While the potential financial upside can be great, there are challenges with underdeveloped health systems, fluid market dynamics, and lack of expertise that can result in failure. One pharmaceutical executive expressed the risk of a one-size fits all strategy for entering emerging markets, "Our biggest mistake was treating emerging markets like mature markets. We were wrong. Pharmaceutical strategies have to fit a country's individual needs and development" [26].

The inability to use established processes for forecasting, market launches, supply chain design and brand strategies all introduce additional risks to the external supply chain. The requirement to adjust to and handle multiple, different strategies depending on the market increases complexity in all functions. The unknows associated with emerging markets increase the variability in forecasted demand compared to established markets. Several pharmaceutical companies have expressed the need to develop more flexible supply chains and accurate forecasting processes to help mitigate some of the risk associated with emerging markets being a major proportion of company sales.

### 1.2.2 Shifting Supply Chain Risks at AstraZeneca

In 2012, AstraZeneca refocused their corporate strategy on "returning to growth through science led innovation" to address the growing number of products reaching the end of their patent life and stagnant market growth. This has led to a significant increase in research and development programs, regulatory filings, new products and market launches. One of the main drivers of the growth is the development and implementation of the 5R framework in the R&D

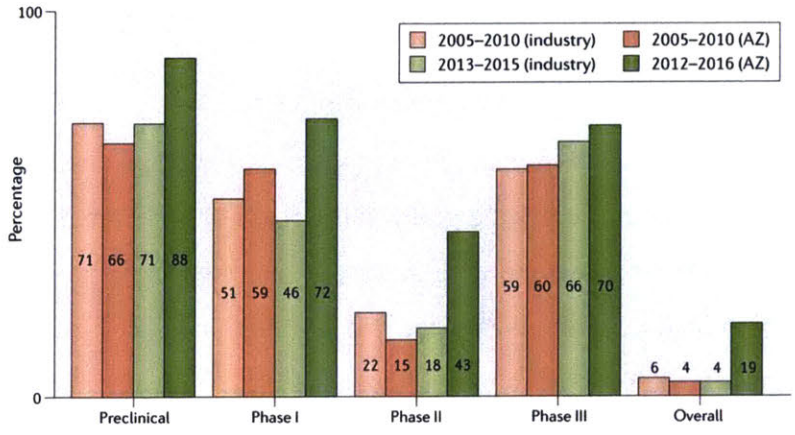


*Figure 3- Project Success Rate by Phase Following 5R Implementation [21]*

organizations and focus on the three main therapy areas. The five Rs are right target, right patient, right tissue, right safety, and right commercial potential. From 2012 to present, AstraZeneca has transformed into the most productive R&D company in the pharmaceutical industry. Figure 3 compares the percentage of products that are successful in each R&D phase. It highlights the improvement of R&D productivity at AstraZeneca after the implementation of the 5R framework and how they are outperforming the industry in each phase, including nearly 5x the productivity overall.

Today, the effect of the 5R framework is exemplified through the healthy product pipeline. With over 150 products in the pipeline, the scope of the development includes New Molecular Entities (NME), life cycle management programs and combination treatments with other products, including products from other pharmaceutical companies. Life cycle management programs are clinical trials to identify new or expanded indications for existing products while combination treatments are collaborations between two different products and can include collaborations with other pharmaceutical companies. The product portfolio is more focused on the three therapy areas which is reflected in clinical trial programs. Figure 4 provides an overview of the extensive clinical trial program for NMEs and lifecycle management programs. An additional 28 combination therapy trials are in progress but not shown. [7]

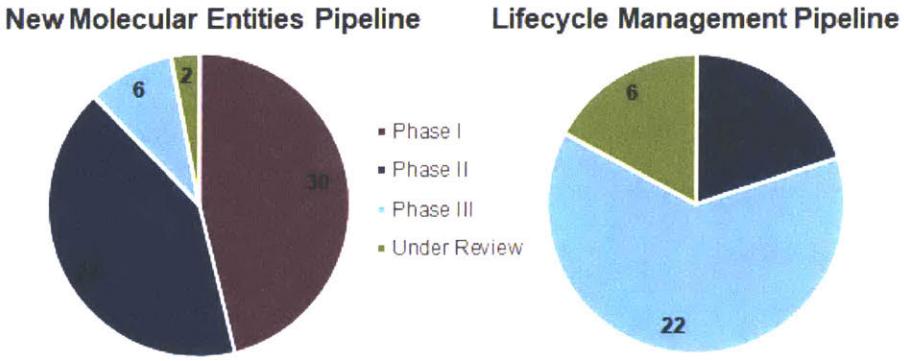


*Figure 4 - AstraZeneca Current Clinical Trial Program*

In 2018, AstraZeneca had 18 regulatory approvals [3] compared to 3 in 2009 [2]. Since the introduction of Breakthrough Therapy designations[1] by the U.S. Food and Drug Administration (FDA) in 2012, seven AstraZeneca products have been granted this designation for accelerated

[1] Breakthrough Therapy designations are awarded by the FDA to drugs that treat a serious or life-threatening condition and preliminary evidence indicates the drug is significantly better than other treatments available in clinical trials.

development. In addition, a total of 20 products were granted orphan[2] designation. These are all clear evidence of the increased strength and productivity of R&D at AstraZeneca over the past six years. Additionally, approximately 50% of the pipeline is within the oncology therapy area. [7] This creates increased risk of demand variation due to the large number of lifecycle management programs and the variation and expansion of the target patient population in the oncology area. The acceleration of R&D growth, intense focus on specialty care treatments and number of product launches has fundamentally changed the supply chain risk profile, generating a new set of challenges GES must manage. The largest of these risks is the potential for sustained or increased levels of long-term demand variability.

When GES was formed in 2006, it was focused on blockbuster primary care drugs. The company was just beginning to outsource more manufacturing and handled on average less than eight regulatory approvals per year. Today, the organization has been coping with massive amounts of change in response to the increased R&D productivity, expansion of active brands and more technically challenging and expensive products. The supply change risk profile has changed due to:

- Increasing complexity of products requiring on average double the Good Manufacturing Practice (GMP)[3] steps and specialty manufacturing processes
- Increasing API costs resulting in excess inventory being a large financial burden
- Shifting to specialty medicine introducing more variability into the target patient pool over the lifecycle of a product compared to primary care treatments.
- Accelerated commercialization due to new regulatory frameworks and desire to reach patients faster

A report published in 2016 by *Drug Discovery Today* analyzes data from twelve pharmaceutical companies from 1995 – 2015. The report indicates that many of the trends AstraZeneca is experiencing related to emerging markets, affordability and a shift towards specialty care

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[2] Orphan Drugs designation is meant to accelerate the development of diagnosis or treatment of rare diseases or conditions that effect less than 200,000 people in the U.S. or would be too expensive to be commercially viable. Regulatory and financial support are available.

[3] Good Manufacturing Practice is the set of systems, practices and policies that are the guidelines for producing pharmaceutical products among many others. GMP is required by drug regulatory agencies to authorize and approve the manufacturing of a product and/or facility.

products are industry wide [10]. While AstraZeneca is ahead of its competitors in R&D productivity, the supply chain, technology and price challenges are critical to address for the future success of the company.

The current operational model of GES does not efficiently handle the updated supply chain risk profile. As the organization begins to stabilize after years of change and adjustments in reaction to shifting industry needs and corporate strategies, the timing is right to step back and examine the processes and operational model to determine what is required to efficiently and effectively meet the needs of the current and future product pipeline. With the goal to deliver maximum value to the patients and provide the stability for AstraZeneca's future operations, GES is in the position to redefine their strategy to become a world class supply chain organization. The development of an operational model that meets the new supply chain risk profile with a focus on flexibility and agility is a critical step.

### 1.2.3 Contract Manufacturing Industry for Pharmaceuticals

Contract manufacturing is a contractual relationship in which a company manufactures a good or material for a specific customer as part of their overall manufacturing operation. These companies are referred to as Contract Manufacturing Organizations (CMOs) and provide manufacturing, R&D and process development services. This type of outsourcing is a common strategy for pharmaceutical companies to defer some of the financial and chemical manufacturing risks to the supplier. In exchange, the company takes on supply chain and product quality risks associated with working with external parties. As the variety of products and volume of demand increase, pharmaceutical companies can find the necessary capacity and technology without requiring new facilities or equipment. This reduces time to market and converts capital investments into a variable product cost. Registered Starting Materials (RSMs) and intermediates are the most commonly outsourced manufacturing processes, with API manufacturing at CMOs continuing to grow.

A 2012 PharmaIQ report on contract manufacturing estimated that 77% of pharmaceutical companies work with CMOs and that for the following planning year (2014), 44% cited controlling operating costs as the most important factor when considering their CMO strategy. The ability to accelerate the commercialization process, reduce manufacturing costs and gain access to specialized technical processes and techniques are among the most cited reasons

companies are increasing their business with CMOs. Another trend that highlights the scale industry growth is the surge in CMOs opening in the Asia-Pacific region, creating a new market of suppliers for pharmaceutical companies to work with. Many pharmaceutical companies altered their strategy to include CMOs in China and India to gain cost advantages associated with lower overhead and labor costs. [22]

Today, rising costs and quality concerns with the Indian and Chinese CMO industries have led to many pharmaceutical companies shifting their operations back to European and North American CMOs. Interviews with three of AstraZeneca's CMOs highlighted that in the 2000s, the CMO industry was primarily concentrated in Europe and North American with these companies investing heavily to meet the growing demand. The shift toward eastern suppliers left them with excess capacity. In the last few years, however, they have experienced a resurgence in demand for their services, requiring companies in some cases to reserve manufacturing capacity up to two years in advance. The suppliers interviewed attributed some of the shift back to the west to quality concerns with the eastern suppliers and the technical capabilities of the western CMOs. These CMOs are the preferred partners to work with in a majority of cases. A large number of small and mid-size customers filled capacity in the 2000s and are still competing for capacity today. These customers typically have 1 – 10 products and are working with the CMOs because they have limited or no internal manufacturing capability and desire their process engineering capabilities. To complicate matters, the CMOs' customers' needs have also changed. The CMOs existing business strategy for working with large pharmaceutical companies centers on utilization of large volume manufacturing assets, annual campaigns and long lead time ordering.

A shift in supply chain and manufacturing strategy in major pharmaceutical companies requires a similar shift in the CMO industry. As a central part of most major pharmaceutical company's manufacturing strategy, CMOs need to be viewed as a critical feature of the manufacturing system to create sustainable change to meet the market needs. Flexibility, agility and technical expertise are all requirements expressed by major pharmaceutical companies to meet the needs of their patients and manufacturing complexity resulting from the industry trends explained in sections 1.2.1 – 1.2.3. Several CMOs have exhibited the ability to create innovative ways of working with smaller companies to meet these changing needs. A combined effort by

CMOs and major pharmaceutical companies is required to create a lasting shift in the CMO industry and move from transactional industry to a partnership model for more critical manufacturing stages.

## 1.3 Problem Statement

As AstraZeneca transitions from a traditional primary care product portfolio to a highly innovative, specialty care portfolio, demand forecasting becomes more critical to ensure that maximum value is added through the external supply network. Employee experiences in the last few years indicate that increase in technical complexity, cost, lifecycle management programs and number of new product and market launches has increased the variability in long-term forecasts. The most visible result is poor inventory performance for new products. This ties up valuable cash in inventory that could otherwise be used for R&D and clinical trial programs. The research hypothesis is that unexpected demand variability negatively impacts the external supply chain and is caused by a combination of the demand forecasting process and supply chain processes and policies.

The purpose of this research is to develop a method to assess the financial and non-financial impacts of demand variability on the external supply chain and identify opportunities to reduce the impact on the external supply chain. Based on discussions with key stakeholders, recommendations should be focused on reducing the impact of demand variability, not a reduction in variability due to the forecasting process. The forecasting process is not in scope because there are on-going efforts to improve the process by GSC&S and GPPS. In addition, the existence of high levels of variability during initial NPI years is a base assumption due to the nature of the pharmaceutical industry and product launches.

The two primary goals of the research are listed below. Specific research objectives associated with each goal are outlined to divide the work into meaningful sub-goals.

- Develop a method to assess and quantify the impact of demand variability on the external supply chain and manufacturing operations
    a. Identify sources of variation that result from internal policies related to forecast utilization and communication

b. Assess the current state supply chains and external manufacturing operations within the case study framework. Identify opportunities for improvement.
c. Utilize external benchmarking and literature review to build a set of test cases for commercial arrangements. Benchmark change management strategies within a supply base

- Identify process improvements and/or strategies for AstraZeneca and external suppliers to mitigate the impact of demand variability.
    a. Develop a set of characteristics that define a successful supplier partnership
    b. Assess alternative commercial arrangements and identify areas to mitigate the forecast variability risk.
    c. Identify opportunities for increased flexibility in manufacturing system

The research objectives and goals break the problem statement into defined questions based on the context and motivation for the research. While not inclusive of all the work completed during the course of this research, it clarifies the areas that are of most interest and require deep study to be able to meet the success criteria outlined in the problem statement.

# 2 Literature Review

This research explores the use of simulation tools and supply chain strategies to measure the impact of the bullwhip effect. This includes connecting demand variability to inventory performance, and methods for mitigating its effect. There exists an extensive body of research on methods for quantifying the bullwhip effect and supply chain simulation methodologies. The intent of the literature review is to generate baseline knowledge on current methods used in each of these areas. Much of the work is focused on simple, two-stage supply chains, which does not capture the network or regulatory complexities that are introduced in most major drug substance manufacturing supply chains. Sections 2.1 – 2.3 summarize the current trends and research to develop a framework to analyze the impact of demand variability and assess potential mitigation strategies.

## 2.1 The Bullwhip Effect: Measuring and Mitigation

The bullwhip effect is a well-documented phenomenon in supply chain management that seeks to explain the increase in demand variability as you move upstream in the supply chain. There is an extensive body of research proving the existence of the bullwhip effect, how to identify it and then mitigate its effects. It has been widely observed that manufacturing industries and supply chains with multiple echelons are at a higher risk of experiencing the bullwhip effect. In the last decade, there has been an increased interest in using analytical methods to help better categorize and measure the impact of the bullwhip effect.

Lee et. al. (1997) provides an overview of the four main causes of the bullwhip effect and five strategies to mitigate its impact. The article cites demand forecast updating, order batching, price fluctuations and shortage planning as the main causes of the increased variation upstream in the supply chain [16]. To counteract this effect, they suggest a framework focused on information sharing, channel alignment and operational efficiency. Lee expands on this research further through a detailed study on the role of information distortion in generating the bullwhip effect [17].

Forecast accuracy and updating contributes to the bullwhip effect through distorting the demand signal to the supply chain. These are initial target improvement areas because they are the responsibility of the customer generating the demand information and ordering and therefore

easier to address since it is internal. Research by Ali et. al. (2012) simulated a two-stage supply chain to study the connection between forecast accuracy and inventory performance. The results of the study indicated that the percentage reduction in inventory levels is less than the reduction in forecast error and the cost savings will be less than the cost avoidance associated with inventory holding [1]. Goodwin addresses the cost saving versus avoidance challenge by expanding the scope of analysis to include indirect costs of forecast errors as well as the limitations of existing metrics [12]. This work expands on the earlier work by Lee et.al. (1993) that measured the total cost of forecast error and identified correlations between different types and sources of error to total cost [19].

### 2.1.1 Mitigation Strategies

Information sharing has been proven empirically to be one of the most effective measures for reducing inventory and cost-control in supply chains experiencing bullwhip. Walmart's Retail Link program is a point-of-sale data summary for suppliers that provides direct access to valuable demand data across many stages in their supply chain. It is one of the most celebrated and cited cases of demand information sharing resulting in positive financial impacts for the customer [18]. Lee, So and Tang (2000) uses analytical models to estimate the value of information sharing in a simple, two-stage supply chain. For supply chains where the retailer bears the full cost of providing reliable supply, the retailer does not experience direct benefits from information sharing. However, the results showed that there are tangible inventory reductions and associated cost-savings at the manufacturers [18]. These cost savings are amplified when lead times are longer. This study provides a strong allegory for the pharmaceutical industry where the drug manufacturer bears all risk associated with stock-out or shortages, but Contract Manufacturing Organizations (CMOs) are involved in some or all of the manufacturing supply chain. A study by Raghunathn (2001) supports similar conclusions for non-stationary demand when point-of-sale data is shared.

Reduction of lead times is the other common method to reduce the bullwhip effect. The reduction in lead time limits the time delay from the actual demand to the supply chain nodes. Direct reductions can be achieved through streamlined ordering processing, manufacturing planning improvements or manufacturing time improvements. In-direct reductions enable shorter lead times, but still require the same amount of manufacturing time. These can be achieved

through dual-sourcing and inventory design. A simulation study of a semi-conductor supply chain by So et. al. (2003) showed that suppliers with variable lead times result in high variability in order quantity and this is exacerbated when demand is also highly variable [25]. Earlier research by Watson (1987) found that when demand is lumpy, like campaigns in pharmaceuticals, the inventory volume and holding costs were increased to be able to achieve similar customer service levels for smooth demand [27].

### 2.1.2 Measuring Bullwhip: Current Methodologies

The increased prevalence of analytical tools in operations research has led to the development of methods to proactively estimate and measure the impact of the bullwhip effect. Combining demand and ordering variance information with simple supply chain design characteristics, models have been developed to estimate the expected variability. There are a variety of methodologies that have been used to measure the expected variance due to the bullwhip effect. For the purpose of this research, analytical and simulation methodologies that seek to either measure the extent of bullwhip or its impact are of interest.

Studies by Chen et.al. (2000) [5] and Fransoo et.al. (2000) [9] provide analytical methods that focus on estimating how much bullwhip a particular supply chain will experience based on demand behavior and supply chain characteristics like lead time. In addition to estimating the expected level of bullwhip, it is also critical to measure the expected impact to understand the potential future benefits of actions taken to reduce the bullwhip. Three studies provide different methods to measure the impacts including information sharing (Li et. al. 2006 [20]), forecasting methods (Campuzano-Bolarin et. al. 2011 [4]) and measuring bullwhip in practice (Jin et.al. 2017 [15]).

## 2.2 Supply Chain Simulation Software

For over 60 years, simulation has been used in manufacturing and business applications and is a widely accepted methodology in operations research. A comprehensive review of academic papers from 2006 – 2010 published in the *European Journal of Operational Research* suggests that the use of simulation in supply chain management and strategy applications is increasing and while discrete event simulation is still the most common application, system dynamics and hybrid applications are becoming more commonplace [14].

This review highlights several key trends in simulation application and strategies in operations research that were utilized during the course of this research. The most critical observation is that discrete event simulation (DES) alone does not achieve the same level of stakeholder engagement as other methods on their own or combining DES with other methods for a hybrid simulation. The use of system dynamics combined with DES can be a powerful tool for providing enterprise-wide solutions, engage a broad range of stakeholders and provide strategic value, not just analytic. [14]

A case study on the Mexican automotive industry highlights the benefits of using a hybrid simulation to improve performance in a complex supply chain. A simulation software was used to develop a tool based on DES and system dynamics to optimize the supply chain for order fulfilment. The study captures how introducing system dynamics into the simulation strategy identifies key variables in complex environment quickly and can be a powerful tool for rapid analysis and stakeholder engagement for strategic changes. [24] Selecting an appropriate simulation software that fits your application is the first step.

An internet search returns over a dozen commercially available simulation software products that are advertised for supply chain applications. Based on feedback from LGO students, product websites and tools previously or currently used within AstraZeneca, five products were reviewed and summarized in Table 1. The observations were collected based on feedback from people who have used the software as well as trying the trial versions of the software packages. The extensive product offering shows that simulation is becoming an increasingly important tool in supply chain management for optimization, performance analysis and strategic decision making.

*Table 1 - Summary of Select Simulation Software Packages*

| Product | Infrastructure Requirements | Common Applications | Benefits | Limitations |
|---|---|---|---|---|
| *FlexSim* | Standalone product with free base product. Excel integration capability, | Manufacturing, healthcare, packaging operations, logistics | Integrates seamlessly with excel, drag and drop model building, strong custom logic capabilities, no coding experience required, mixed simulation methodologies available. | Limited demand analysis capability, high volume of objects crashes software |
| *Simulink* | MATLAB add-on, coding based interface, start-up resources provided, excel integration is through MATLAB inputs | Engineering systems, control systems, model based design | Strength is in multidomain/dynamic systems, meant for iterative design, extensive analytic capability | Strong coding experience required, may be too detailed for strategic work, not commonly used for supply chain applications |
| *Llamasoft* | Suite of software products targeted at specific applications. Visualization and Supply Chain Guru are most applicable products | Targeted for supply chain applications – Supply Chain design, planning, and visualization | Data aggregation, what-if modeling, ease of visualization, supply chain optimization, single software package for optimization and simulation | Free trial not readily available, forecast analysis cannot be done in package, requires significant data sources |
| *AnyLogic* | Business focused simulation software, cloud compatible | Business processes, manufacturing, marketing | Drag-and-drop environment, discrete event, agent based and system dynamics capability | Expensive product, steep learning curve |
| *Process Simulator* | ProModel product, model building can be done in Visio, integrates closely with excel | Manufacturing, planning, workflow, value stream map | Extensive tutorials, ease of use, flexibility with flow items, strong animation | Trial version is extremely limited, minimal analytic capability |

## 2.3 Engaging the supply base – Transactions to Partnerships

A supply chain partnership is a relationship between a supplier and their downstream customer in which both parties obtain greater value through close integration. A transactional relationship, one based on a contract, is the most common type of relationship seen in supply chains and in most cases is sufficient to meet the needs to both parties while running successful businesses. A supply chain partnership is most beneficial when the manufacturing process is complex, the overall system is dynamic where a high level of information exchange and interaction between parties results in higher performance based on the defined set of metrics. A partnership is indicative of more than just collaboration. A collaborative relationship is a precursor to partnership between two firms.

A review of the literature exhibits a strong understanding of the benefits of supply chain partnerships, there is limited information defining the specific characteristics of a partnerships and how to develop one. He, Gallear and Ghobdian made a strong case that trust, commitment, interdependence, shared meaning and balanced power are the key characteristics of a supply chain partnership [13]. While the case study presented supports their conclusions, those five traits are hard to define and understand how to develop. For this reason, external benchmarking was completed to better understand how companies develop partnerships and achieve the transformation through change management practice. Discussions with the suppliers indicated that there were two aspects to engaging and developing additional value in their supply chains – the relationship and continuous improvement with suppliers. Results are summarized in Table 2.

*Table 2 - External Benchmarking - Key Takeaways*

| **Company 1 – Supply Chain Logistics & Sourcing Company** | | |
|---|---|---|
| *Relevant Context:*<br>- Do not own any manufacturing operations or facilities, but handle all aspects of a supply chain for customers<br>- Supply base is typically "low-tech"<br>- Supplier engagement and development is a major part of business<br>- All relationships are transactional, but develop suppliers' capabilities to make them more competitive | *Supplier Engagement/Relationship:*<br>- Mindset is one of the most important factors in selecting suppliers to work with<br>- Open book costing and forecasting via digital modes it a requirement for partnership<br>- Transparency is key to battle "why invest" when there are not long-term contractual commitments<br>- Customer's ability to clearly communicate what they see as a competitive advantage is important for the suppliers | *Continuous Improvement in supply base:*<br>- "train the trainer" – significantly more beneficial to empower the supplier to make their own changes<br>- Access to financing helps get engagement for technology improvements or projects<br>- Shifting suppliers from "task executers" to "competitive advantages" helps them be proactive with improvements<br>- For anything related to Industry 4.0, build in the infrastructure initially to go big, but start really small and gradually expand |
| **Company 2 – Retail – Apparel/Footwear (Major)** | | |
| *Relevant Context:*<br>- 100% outsourced manufacturing<br>- Manufacturing base almost entirely in Asia<br>- 2 Divisions, each has different manufacturing strategies and requirements for types of suppliers they work with<br>- extremely competitive market and competition for suppliers also exists | *Supplier Engagement/Relationship:*<br>- Open book costing: to be financially successful, our suppliers also need to be financially successful<br>- Several face-to-face meetings<br>- Trust and loyalty are the foundation for relationships, transparency at all levels and data sharing are how this is accomplished<br>- Capabilities and the ability to maintain them is more important than cost for selecting suppliers | *Continuous Improvement in supply base:*<br>- Dedicated team helping suppliers be efficient and productive through control of company's inputs (i.e. level load orders, utilization)<br>- On-site engineering team to support suppliers, act as consultants<br>- Company is active participant in operations even though doesn't "own" any of the manufacturing<br>- Assist with training and funding, but suppliers own all improvements |
| **Company 3 – Aerospace Manufacturer** | | |
| *Relevant Context:*<br>- Multi-tiered supplier network<br>- Regulated environment<br>- Cost challenges with suppliers in the past<br>- Multiple programs, so suppliers may interact with several different people or products<br>- Unbalanced margins between supply base and customer | Supplier Engagement/Relationship:<br>- The "why" for suppliers is critical<br>- Sharing KPIs openly improves communication and transparency<br>- Sometimes you just need to exit a supplier regardless how long you have been working with them<br>- Branding of initiatives helps achieve uniform communication<br>- ERP transparency helps suppliers be proactive and identify improvements | *Continuous Improvement in supply base:*<br>- Cost reduction programs with a tool box and significant support to assist suppliers to meet targets<br>- Technical approach to "should cost"<br>- On-site presence by several functions is a key enabled of joint continuous improvement<br>- Digital data is key to understanding true operational performance |
| **Company 4 – Retail – Apparel/Outdoor Goods (Mid-size)** | | |
| Relevant Context:<br>- Mixed of branded and vendor products<br>- Small customer for the CMOs<br>- Co-op organization | Supplier Engagement/Relationships:<br>- Stick with "little guy" during start-up because it build loyalty in the long run<br>- Seek to be the "preferred customer" for the CMOs; flexible in operations and planning so they come to them first when there is available capacity<br>- Use a trial period for new CMOs<br>- Quality always trumps cost | *Continuous Improvement in supply base:*<br>- Work on improvements as a mechanism to improve supplier operations since don't have negotiating power to change their operations<br>- Need to clean up operational performance internally before you can ask your suppliers to do more |

The external benchmarking was a great opportunity to put some experience behind what is commonly shared in literature and industry regarding developing partnerships and strengthening organizations. Building trust through transparency, open communication and information sharing are not unique to supply chain operations but understanding the "how" behind these concepts is critical to be able to put these concepts into practice. The key takeaways from the four companies are summarized below.

- A clear value proposition for suppliers on why they should change behaviors is critical for success. This includes understanding what makes them competitive in the eyes of their customer.
- Branding a change program is a powerful change management tool because it enables consistent communication across all levels, helping to support universal understanding
- Figure out what you do as a customer that causes problems for your suppliers
- Every company mentioned that cost was not a major factor when selecting suppliers they would be in more strategic relationships with.
- You cannot live by a contract in a partnership. There needs to be flexibility, which cannot be written into a supply agreement.
- Understanding your suppliers' operations is key to understanding how to best leverage them and actually understand their performance. Data sharing is a requirement and it should only be data that is interpretable and useful (not all of it).

The benchmarking takeaways will be critical for understanding the non-financial impacts of demand variability and potential mitigation strategies. They also address some of the key research questions around what it means to be a strategic supplier and how to develop these relationships. Supplier engagement can be one of the most difficult aspects of supply chain management, but also one of the most impactful. The external benchmarking exercise highlighted how investing in supplier relationships and the tools and infrastructure that enable it positively impact the supply chain and manufacturing operations across multiple functions.

# 3 Approach

The research goals of this project are both diagnostic and strategic in nature. With the environment in pharmaceuticals and AstraZeneca changing rapidly, there is a need to develop an understanding of the existing processes, methodologies and operations used in forecasting and supply chain execution to be able to effectively develop a method of analysis and define strategic opportunities. The research was separated into three phases – data collection and current state analysis, modeling and simulation, and test case analysis and recommendations, which are summarized in sections 3.1 – 3.3. The phases help guide the research process to prevent any existing predispositions or bias internal to AstraZeneca or within the supply base from coloring the research.

A case study approach is utilized to narrow the scope to allow for depth of analysis rather than breadth across the entire product portfolio. Two primary products and an auxiliary product were selected to be included in the research. The products were selected based on an initial review of the characteristics of high volatility products and feedback from stakeholders across multiple organizations. An overview of product characteristics is summarized in Table 3. Product A and B are the primary focus of research, while Product C provides alternative product and supply chain characteristics for qualitative comparison.

*Table 3 - Summary of Case Study Product Selections*

| Product | Therapy Area | Supply Chain Characteristics | Product/Market Characteristics |
|---|---|---|---|
| Product A | Oncology | new supply sources; divergent supply chains at formulation; ramping down production for one formulation type, no upstream ownership by suppliers | Life-saving treatment; Extensive on-going clinical trials, several new indications launched, two formulations; risk adjusted long-term forecasts; historic extreme variation in demand (over +/- 50% in volume) |
| Product B | Cardiac | Dual sourced at all stages; 4 API suppliers; strict supply contract terms; large volume commitments in supply contacts; significant flavor management[4] | Life-savings treatment; High cost-of-goods, technically complex (+20 registered reactions), significant demand shift in 2015, chronic underperformance of long-term forecast |
| Product C | Metabolic | Majority of supply chain is internal to AZ with intermediate stages outsourced; device supplier; | 3rd generation product, device critical to patient experience, extremely cost-competitive market, non life-saving treatment |

[4] Flavor management is the management of different varieties of a product based on where it is manufactured and what markets it can be distributed based on regulatory filings.

The case study framework provides the focus to collect relevant data through process reviews, statistical analysis and employee interviews to define the current state of manufacturing and supply chain operations for AstraZeneca. The "voice of the supplier" is the other major source of data. With such a large percentage of the supply chain outsourced, understanding the role of the supplier in the operation and the relationship with AstraZeneca is a critical data set. Three suppliers were selected to be included in this research henceforth referred to as Supplier A, B and C. Basic overview information on each supplier can be found as part of the interview summary in Table 7 in section 4.4. The suppliers were selected because they are responsible for manufacturing material for Product A and B, have a significant volume of manufacturing for AstraZeneca and are viewed as strategic suppliers by GES.

## 3.1 Data Collection and Current State Analysis

This stage is exploratory in nature, covering the breadth of operations that interact with, support or contribute to the external manufacturing operations. Forecasting, operations and supplier relationships are critical pieces to understanding the supply chain and how it reacts to demand signals. These three functional areas were identified through the literature review and discussions with critical stakeholders as either sources or recipients of forecast variation. An in-depth study of internal policies and procedures at AstraZeneca is utilized to define the current state for the three case study products. Product A and Product B were also analyzed from the supplier's perspective to capture the manufacturing planning, supply chain operations and relationship aspect for the two products.

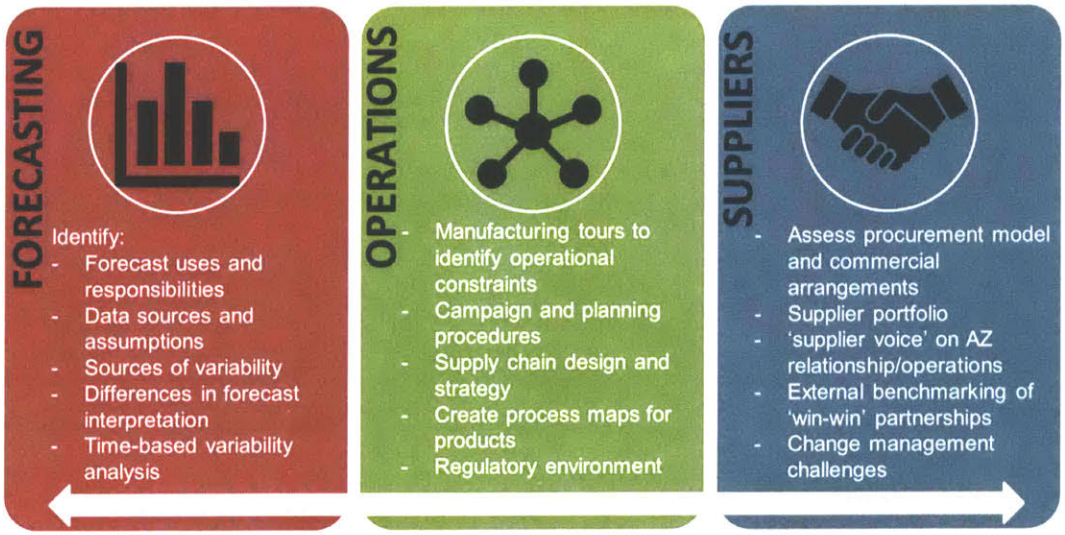


*Figure 5 - Current State Analysis Framework*

Figure 5 identifies the key research areas within each function that focus the current state analysis. This data is aggregated and summarized through a series of process maps, interview tables and observations to be used as evidence in the impact assessment. The outcome of the analysis provides the data required for the analysis of demand variability and the baseline operation to test potential improvements against. A bulk of the research time is spent in this phase on data collection, aggregating and mapping to allow for ease of interpretation, access and use in later phases of research. The outcome is a valuable body of knowledge for the organization, providing a wholistic view of the supply chain and manufacturing processes that has been operating in a siloed manner.

The supplier relationship function could not be assessed and understood through solely reviewing procedures and policies internal to AstraZeneca. Employee interviews were completed with Suppliers A, B and C and site visits were made to Supplier A and B. These interviews were with business development leaders, project managers and relationship managers at the suppliers and example types of questions that were asked are listed below. Exact questions were tailored to the individual and were provided a minimum of three days prior to the scheduled interview.

- What is the company's competitive advantage or value proposition?
- Are there any trends or major challenges the pharmaceutical Contract Manufacturing Organization industry is facing today compared to a decade ago?
- Can you provide an overview of what the operational model the company uses for working with AstraZeneca? Is this the same or different from other customers? How is performance measured?
- Reflecting on the working relationship with AstraZeneca, what works well? What could be improved?
- What are some of the challenges of launching a new product from a supplier perspective?
- How do you use the forecasts provided from AstraZeneca? How do changes impact operations?

In addition to these interviews, on-site manufacturing tours, and attending various meetings (on-site, at the Macclesfield campus or virtual) provided context to characterize the relationship between AstraZeneca and each of the suppliers. These additional activities also provided useful

understanding of how the relationship might differ across functions and levels in the organizations.

## 3.2 Modeling and Simulation

The intent of this phase is to develop a methodology for measuring the impact of demand variability on the external manufacturing operation. A simulation strategy and tool are used to develop a model that simulates how the forecasts interact with the supply chain design. The model will be designed for high level estimates of the financial impact of supply chain strategies through tracking the value of the API inventory stock. The model should be easily reconfigurable and at a high enough level that it can be used for basic analysis across any small-molecule brand that GES manages. Ease of use and understanding were traded-off for accuracy which follows with the goal of this being a decision assist tool. The model's key input should be the forecast data and supply chain design, while the primary variables are lead times, as these are the main areas that can be controlled by AstraZeneca.

A clear understanding of the forecasting supply chain design processes provides the foundation for the models, including Product A and B case studies as the base case examples for use in model verification and interrogation. Due to data limitations and the non-standard process for determining actual material purchase order volumes, a direct model to actuals comparison could not be used as a verification method. As an alternative, the historical ordering and inventory trends were compared to the output and the difference between the models output and actuals was captured and reviewed to see if manual interventions completed could account of the differences.

The deliverable from this phase is a tool that enables users to quickly understand if a change in forecast or supply chain design would have an impact on the entire system. Since inventory is a standard financial measure, a "dollar per day" value can be placed on lead time improvements for a specific brand. This approach not only allows the user to gain a systems perspective on the supply chain operations, but also can be useful in estimating potential financial impact of an operational design change on inventory. Previously, this would have been difficult of AstraZeneca to estimate in a repeatable and scientific manner.

## 3.3 Test Cases and Recommendations

The analysis and recommendations are focused on opportunities to alter existing policies, change ways of working and strategies to mitigate the impact of demand variability. There are two sources of test cases for future analysis; opportunities identified in the demand variability impact assessment and concepts from the case study products' teams. In most cases, these test cases required a supplemental analysis model for forecasting to modify the inputs into the simulation. The three primary test cases are described in Table 4.

*Table 4 - Test Case Commercial Models*

| | Concept | Potential Benefit |
|---|---|---|
| Gradual Volume Commitment | At defined lead times, commit to a certain percentage of the expected demand. The volume builds over time, but there is also the option to not order if the expected demand is lower. | Does not allow for reductions in volume, but also commits to a lower initial volume. The commitment schedule and volumes and be closely tied to demand scenarios. |
| Fixed +/- Model for API | Commit to a given volume, but later can adjust by a certain percentage up or down. Intermediates must be ordered or manufactured to cover the high side of this range. | Only committing to the lower side of the range and the suppliers take the burden of holding stock to allow for flexibility. |
| Reduce API Leadtime to match short-term forecast horizon | API lead time is approximately 12 months. Use inventory design to allow for reduced lead time at a higher per kg cost | Short-term forecasts can be used for ordering, supply chain is more reactive to changing demand for new products |

The test cases act as a proof of concept for the tool and the strategies. The recommendations are developed based on both the financial and non-financial impacts identified during the current state analysis and represent opportunities to reduce the impact of demand variability. Strategic recommendations focus on designing the overall systems for flexibility and agility. The recommendations are limited to two to three ideas to allow focus and depth of the development. For each recommendation, a pilot program will be outlined as a short-term implementation plan and definition of potential future work. Recommendations should represent the findings from the total body of work and are not limited to those where a financial benefit can be clearly estimated. The recommendations should support, if applicable, other strategic decisions or focus areas for the AstraZeneca and/or GES 2025 vision.

# 4 Current State Analysis

Since the formation of GES in 2006, the responsibilities, scope of work, number of brands and number of suppliers have expanded. The processes, team structures and responsibilities have been refined to enable GES to integrate effectively with downstream nodes in the supply chain and ensure patients have access to life saving medicines. The goal of the current state analysis is to adequately capture how the dynamics of the external operations relate to and are impacted by the internal operations and processes. A systems perspective is used to capture the end-to-end operation, but the primary focus of the process and manufacturing analysis is on the external drug substance manufacturing stages, ending with API manufacturing. The systems approach to the analysis is consistent with the future vision of Global Supply Chain & Strategy (GSC&S) of an integrated and synchronized supply chain with a digital backbone.

The data for this analysis was collected through a review of process documentation, internal presentations, supply chain maps, brand strategies, forecast data, employee interviews, supplier interviews and manufacturing tours. In addition to these physical data sources, participation in several supply chain workshops throughout the internship for the three case study brands allowed for cross-functional review of the system design and reactions to variation in long-term forecasts, including supplier inputs on several occasions.

## 4.1 Manufacturing and Supply Chain Operations

Drug substance manufacturing is the set of chemical manufacturing stages that generate the API, while formulation and packaging make-up the drug product manufacturing stages. This analysis captures the end-to-end operations, with a particular focus on the drug substance manufacturing stages as they make up the most significant portion of AstraZeneca's external manufacturing operations. To-date there has been limited focus on the end-to-end operation due to the organizational silos that divide the operation between the internal and external manufacturing stages. The silos extend to the technical teams that support manufacturing as well. While drug product and drug substance manufacturing require two very different skill sets and knowledge bases, end-to-end mapping can highlight inefficiencies or potential improvements that were not evident when looking at the manufacturing operation as two separate systems.

There are several key operational attributes that apply to a majority of drug substance manufacturing that are useful to understand prior to looking at the product specific systems and complexities. Most drug substance manufacturing at CMOs is accomplished through large volume campaigns in which there will be several batches per campaign on a single manufacturing train. All of a product's demand for a given annum could be produced in one campaign. Annual campaigns allow the CMO to reduce their equipment downtime by minimizing equipment changeovers. A changeover can take up to three weeks for cleaning and reconfiguration of the manufacturing units. The operational savings from the large batch/large campaigns are also passed on to the customer through a reduction in the per unit material cost.

Products are validated by regulatory agencies on specific manufacturing trains. A manufacturing train is a series of assets, such as reactors and driers, that are linked by piping. It is feasible to validate material manufacturing on additional manufacturing trains but requires additional regulatory filings and validation campaigns. If a manufacturing stage requires multiple reaction phases, the material would need to be validated on any trains that are used. This type of campaign is operationally challenging because it is not always feasible to synchronize processing across the required manufacturing trains. The total manufacturing time increases because of inefficiencies associated with scheduling phases separately and linear processing.

GES and AstraZeneca defer to the CMOs for manufacturing planning and execution, but maintain control of the relationships with each of the supply nodes. This includes controlling the movement of materials between the nodes. The desire for this level of control originates from the quality concerns associated with outsourcing manufacturing and can be seen in the process maps.

For the operations analysis, Product A and Product B were reviewed in-depth. The manufacturing process and supply chain were mapped starting with registered starting materials (RSM). These are the first compounds subject to GMP requirements and included in the regulatory filings. The final detail step included is packaging. On the map, the contractual lead times and the estimated manufacturing times when applicable are provided as well as information regarding any conversion steps required prior to manufacturing the final product for a stage. Figures 6 and 7 show the process maps for each product based on their 2018 configuration.

# PRODUCT A Supply Chain and Manufacturing

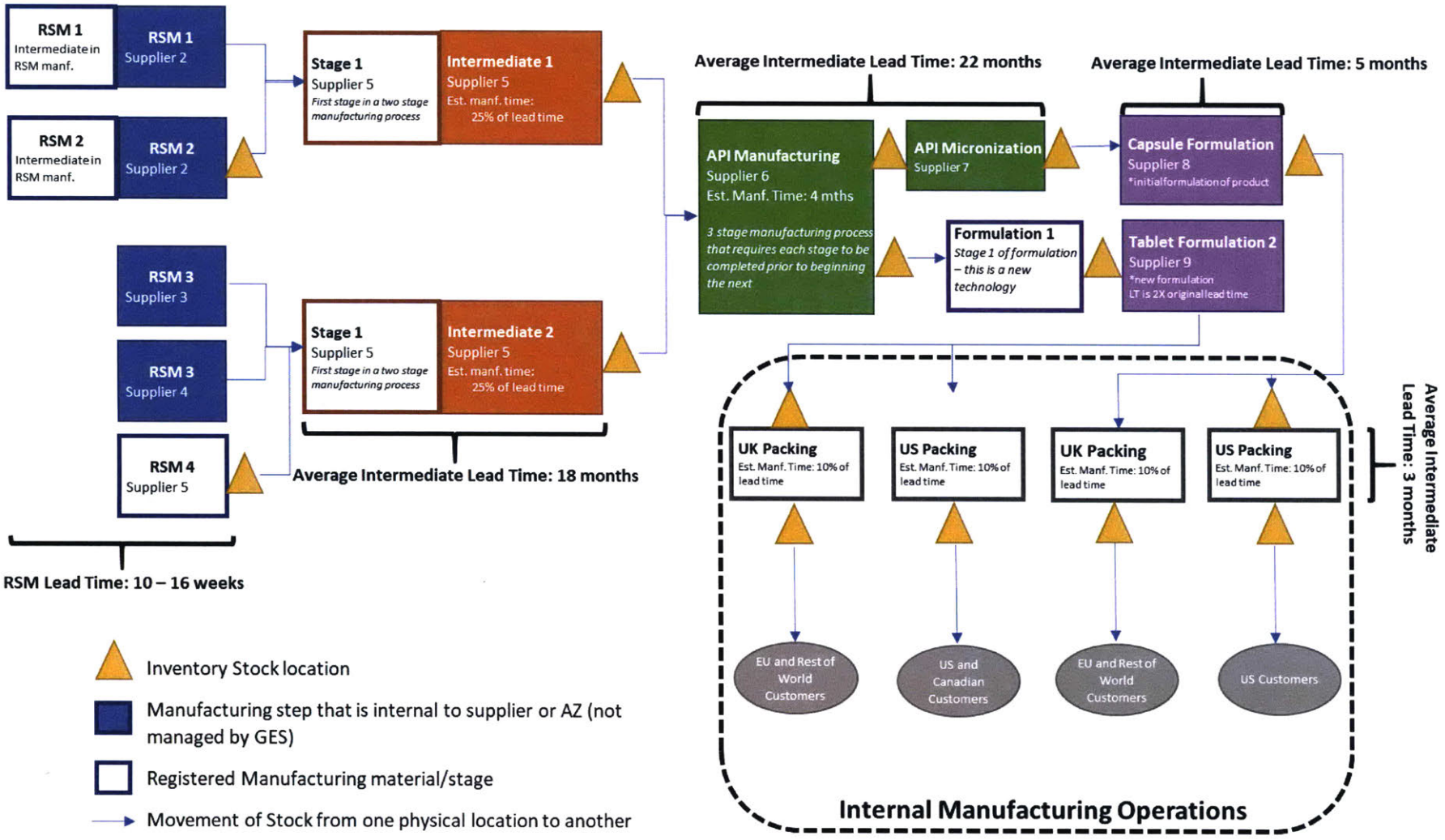


*Figure 6 - Product A Manufacturing and Supply Chain Process Map*

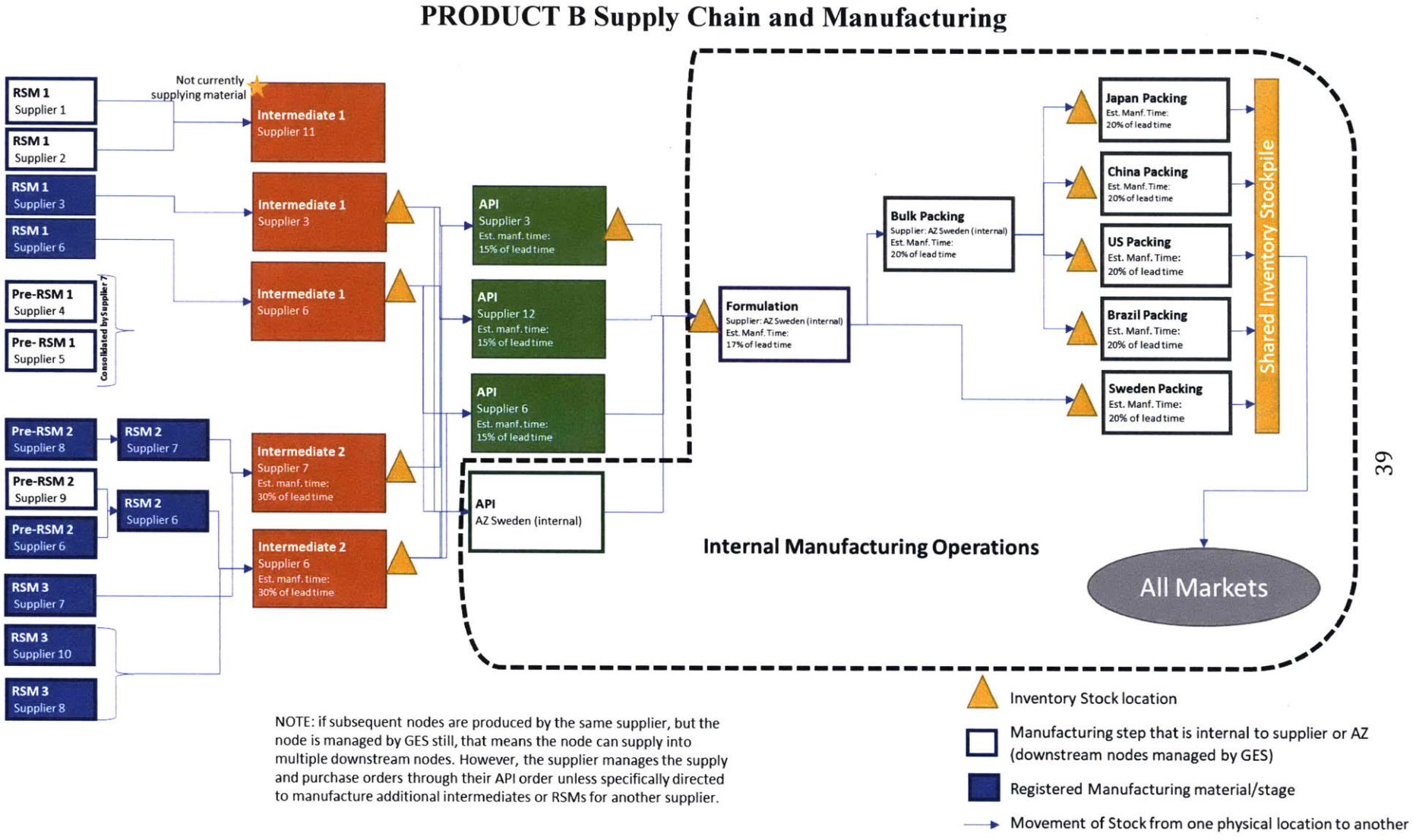


*Figure 7 - Product B Manufacturing and Supply Chain Process Map*

The process maps highlight some of the manufacturing and supply chain challenges associated with Product A and Product B. Product A is still relatively early in the product lifecycle and dual sourcing activities are just beginning. Flavor management does not have a major impact on operations at this time. There are several multi-phase manufacturing stages, including the API conversion stage which is three campaigns within the one annual campaigns. The API is considered a high potency product requiring additional health and safety measures. Only specific manufacturing assets designed for high potency reactions can be used to produce this material. The CMOs are more capacity constrained in these assets due to the number of high potency products increasing in the market. The API volume requirements for same dosage volumes are reduced, so the larger reactors are not required for these types of products. There is additional complexity from having two types of formulation. This separates the supply chain at formulation with different manufacturing processes, regulatory filings and suppliers.

Product B is a more challenging product from a technical perspective as it has over 30 GMP steps in the drug substance manufacturing process. It also has larger demand volumes and experienced several step-function changes in demand over the last five years. For this reason, the number of suppliers for each material is increased and flavor management is extremely complex. The net lead times for a synchronized manufacturing system are over 480 days for drug substance manufacturing and an additional 100+ days for formulation and packaging. When considering the use of annual campaigns and limited communication across the nodes, the lead times increase even more putting the net time from RSM manufacturing start to product availability at a distribution center at over three years. Additionally, the supply contracts at several nodes are inflexible, adding network complexities for allocation of manufacturing volumes across the nodes.

The process mapping exercise highlights the supply chain and technical processes associated with manufacturing as well as the regulatory framework for the operations. The operational strategy for GES is exhibited through the design and execution of the supply chains. While the process maps are for the 2018 state of operations, the previous and future states were reviewed to understand the strategies and mechanisms for changing the design to meet future product needs. For increases in high-side demand, which is the best-case scenario in the forecast, AstraZeneca uses capacity acquisition as their primary method to adjust in significant changes in demand

volumes. This is exercised by purchasing available capacity, exercising options at existing suppliers, renegotiating supply agreements to secure higher capacity or dual sourcing a certain stage. For products that grow to or are expected to exceed certain market value, dual sourcing is a requirement. This is one of the reasons Product B is dual sourced in many stages.

Product C experiences supply chain complexity due to device manufacturing and an external supplier for formulation and packaging. The drug substance manufacturing is internal to AstraZeneca and the integration of the device and product formulation occurs at an external supplier. Devices have been particularly challenging because the technical complexities are mechanical, a different regulatory framework is used, and the manufacturing process is completely different. The complexity of integrating the device and API is the responsibility of the external supplier, which is the most inflexible of the supply nodes. The formulation supplier deals with the complexity of the device manufacturing and demand variability. Unlike with Product A and B, AstraZeneca cannot mitigate variation through holding inventory internally in the later formulation and packaging stages for Product C. The Product C supply chain is experiencing similar impacts due to demand variability compared to Products A and B, but requires alternative mitigation strategies.

Manufacturing tours of three facilities that support manufacturing of products A, B and C were done to observe different phases of drug substance and drug product manufacturing. Three trends stood out - the manual nature of the operation, lack of digital infrastructure and the siloed nature of each manufacturing node. Formulation and packaging are highly automated processes since the rate, volume and repeatability of work allow for simple automation. Automation has been in drug product manufacturing for over two decades and allows for ease of digital infrastructure for data collection and near real time performance metrics. Drug substance manufacturing facilities appear older, manufacturing assets are larger and there is limited electronic data collection. A changeover requires disassembling piping, sanitizing and then reassembling, with most of the flexibility in the manufacturing system design and configuration coming from re-piping lines and valves. Changeovers can take up to three weeks and the cost of this downtime is included in the total campaign cost. There is little incentive for the CMOs to improve their changeover times, but it does contribute to the facilities' capacity constraints.

Drug substance manufacturing technology has not changed significantly in the past several decades. The tours highlighted the same types of large-scale reactors and facility infrastructure that would have looked very similar in the 1980s. This extends to the collection of manufacturing and quality data. There is a significant amount of data collected for each material batch for compliance purposes. While electronic batch records (e-batch) are beginning to become more common in drug product manufacturing, the use of e-batch records is rare in drug substance manufacturing because of regulatory concerns and the investment in infrastructure required that does not directly improve manufacturing costs. The use of electronic data for manufacturing process information instead of quality data can be a powerful continuous improvement tool and enable near real-time manufacturing and performance insights for the entire supply chain. The motivation for building a digital data collection infrastructure for uses other than compliance and quality uses does not exist. This would generate a valuable dataset for AstraZeneca and the CMOs to use for process improvements and understand in greater depth asset utilization in the facilities.

The final reflection from the manufacturing tours is the limited supply chain knowledge each of the manufacturing nodes has available to them. AstraZeneca controls almost all of the material movements and inventory design for both Product A and B. This control extends to manufacturing data and process information as well. The lack of information from the upstream and downstream nodes manufacturing plans directly prevent any synchronization efforts of the overall manufacturing plan by anyone other than AstraZeneca information. Without a digital infrastructure, this level of information sharing is difficult. Risk management at the site is difficult due to the different supply chain nodes lacking direct communication channels and limited data availability. AstraZeneca is missing potential improvement opportunities based on the suppliers' knowledge to improve the end-to-end operation.

There are robust technical and quality procedures in place to execute the drug substance manufacturing at CMOs. AstraZeneca successfully tech-transfers products from labs and facilities within the company to these third parties and has an experienced technical team that supports process improvements. While this provides meaningful improvements to products throughout their lifecycle, many changes require regulatory actions that are time and resource intensive. There are additional steps that can be taken in the area of digital monitoring and

transparency to improve the end-to-end manufacturing operation with a focus on stability, flexibility and synchronized operations that would not require regulatory actions.

## 4.2 Forecast Methodology and Process

Forecasting is the responsibility of the commercial organizations within AstraZeneca. The markets and brand teams provide necessary inputs based on market intelligence, sales performance, product launch schedules and clinical trials among other sources. There are three types of forecasts within AstraZeneca that are used for manufacturing planning – two long-term forecasts and a short-term forecast. In 2015, it was determined that Global Portfolio & Product Strategy (GPPS) organization would take an active role in forecasting for NPI. This introduced the second type of long-term forecast.

- *Short-Term Forecast:* this forecast has a time horizon of 0 – 24 months and is generated by the marketing companies and then aggregated by brand. It provides guidance for manufacturing planning to ensure supply is guaranteed and minimize stock-out risks. The forecast is updated monthly and has established metrics for accuracy. GPPS provides strategic guidance for NPIs starting 18 months prior to product launch.
- *Long Range Plan (LRP):* This is the long-term forecast generated by the marketing companies and then aggregated globally by brand. For large markets, this forecast can cover up to a 10-year forecast horizon, but the exact length depends on the market. This forecast exists for all products and is used for capacity planning and budgeting. The forecast is in units of share pack level, meaning it is based on the estimated volume of sales. Performance to the LRP is a factor considered for marketing company bonuses.
- *NPI Long-Term Forecast:* This forecast is generated bi-annually by GPPS in June and December only for products (not brands) that are designated as NPI. The forecast is used for supply chain design and market launch. It is a 10-year forecast horizon and forecasting begins 5 years prior to launch and continues until the product is no longer designated as an NPI. Each version has a high-side and base case volumetric forecast.

The short-term forecast is integrated into the manufacturing planning systems for use in formulation and packaging and is also the forecast that is used for measuring forecast accuracy. GPPS is not responsible for generating this forecast but does provide input for NPIs to the marketing companies. GES can use this forecast for suppliers' whose manufacturing lead times

are within the forecast horizon. However, the lead times for API manufacturing planning are over 24 months when you include the average 18 month lead time for API manufacturing and the formulation and packaging lead times. For this reason, the NPI Long-Term forecast is used for NPI products and then once they have matured and are no longer designated NPI, the long range plan forecast is used for ordering. Since the focus of this research is on demand variability for NPI, from this point forward, any reference to "forecast" is referring to the NPI Long-Term forecast generated by GPPS.

Figure 8 shows the process of forecast translation. All of the forecasts are generated in volumes of final product units. A single manufacturing unit (SMU) is a pill, vial, syringe, capsule etc. and is the bulk product measure used in forecasts for final products. This eliminates the complexity of all the packaging configurations across markets and provides a common unit for the forecast. The forecast translation is the process of taking a SMU volume and converting it to the relevant API, intermediate and RSM volumes at each of the manufacturing nodes.

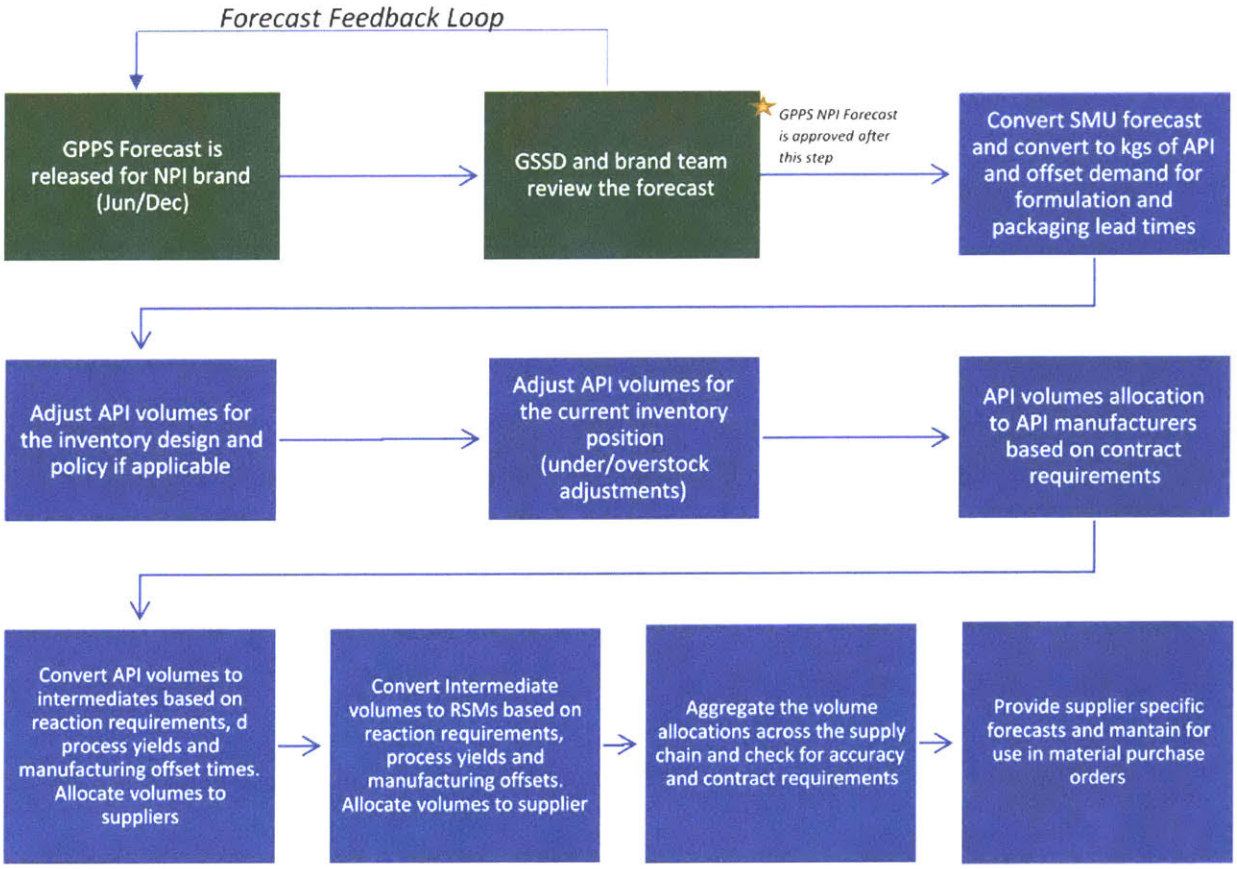


*Figure 8 - NPI Long-term Forecast Translation Process*

The forecast translation process is a method that was developed based on the experience of individuals in GES managing demand requirements for external suppliers. The blue boxes indicate the process steps that GES has the responsibility for and the green boxes are the responsibility of other organizations. For NPI, this process is the mechanism for changes in long-term demand to get communication throughout the supply chain. The outcome of this process is frequently the impetus for major strategic design changes such as dual sourcing, securing additional capacity, reducing capacity or redesign of the system and contracts in cases of significant volume reductions.

The use of a long-term forecast for manufacturing planning is a challenge due to the inherent inaccuracy of predicting pharmaceutical demand early in a product's lifecycle and more than two years in advance of the demand consumption. With Products A's and B's contracted lead times, even if the manufacturing system was synchronized, it is still over two years from when an API manufacturing commitment is required and the final packs are ready for distribution. Considering RSM and intermediate manufacturing, inventory stock pockets, annual campaigns and distribution time, it can be three years before an API volume commitment is made to when the product is available for patients. The introduction of GPPS and the NPI forecast has helped improve the accuracy of long-term forecasts for new products and GSC&S has taken considerable measures to improve short-term forecasting to improve overall accuracy and performance to the forecasts. However, there are three areas in the process that are susceptible to an increased risk of demand variability that are not being addressed– non-standard translation process, limited feedback and inconsistent understanding of forecast assumptions.

Asset planners within GES are responsible for the long-term planning and support Supply Chain Leads (SCLs) with strategic supply chain analysis and decisions. The steps to convert the forecast to the individual material volume requirements are determined based on the chemical recipe, process information and manufacturing yields. Internal policies and the Global Supply Planner (GSP) determine the inventory design for policy and safety stock. For NPI, 12 – 18 months of API policy stock are required per the business continuity policy and it is re-evaluated annually based on the average monthly demand. Policy stock is the volume of material that is meant to secure supply to the patients in the event of an unforeseen disruption to the supply chain. The volume of policy stock id defined as part of the Business Continuity Plan (BCP).

Asset planners collect all of this information for each of the brands that they manage and utilize a brand specific excel spreadsheet to take the forecast and convert it to the material required for each stage in manufacturing. Using supply contract information, volumes are allocated to the different suppliers. This process is manual, and each asset planner uses a slightly different excel sheet format and calculation sequence to execute the translation process. In many cases, these excel sheets are inherited from the previous asset planner for a given brand.

The non-standard nature of the process and the ability to customize a brand's calculation sheet based on the asset planner was acceptable when there were only a handful of new products and the supply chains were not as complex. The workload for asset planners to manage the complexity and allocation of material volumes has greatly increased. Managing these NPI forecast translations can take several days and then sometimes additional weeks once a forecast update is released to determine the adequate course forward if there is a significant change in demand volumes.

While GES is the customer of the forecast and use it for significant supply chain design decisions like contract and purchase order commitments, there is not a clear feedback loop for GES to share the impact of forecast changes on the system. Any feedback currently is given informally and relies on a good relationship between the GSSD, GPPS point of contact and the GES team. These informal information channels are increasing in numbers and strength due to product complexity requiring more frequent cross functional interactions. However, the lack of a formal feedback mechanism on the impact of the forecast makes it difficult for employees at any level within GES to speak up if they see a risk or issues associated with a change in demand. The accuracy of the NPI forecast is not measured and the only indication of poor forecast accuracy is API stock levels differing from the planned volumes.

One consequence of the informal feedback is a lack of clarity around the assumptions associated within each forecast version and what scenario it represents. GES lists the assumptions in the data sheets provided and discusses them with the GSSD. Further communication of the assumptions depends on the consistency and format of forecast discussions between the GSSD and other parties, which for an asset planner is frequently an email. In addition, the assumptions are typically provided as a laundry list accompanying the forecast. The assumptions and scenarios that are used to generate the forecast are not consistently

understood across different roles and organizations within operations and therefore there is a lack of consistency in the exact assumptions and risks associated with a forecast to the suppliers. Each forecast version has a high-side volume, but not every high-side forecast represents the same type of scenario. This introduces additional inconsistency in understanding by having the high side forecast scenario representing different types of assumptions across different brands.

The forecasting process is systematic, meaning it can be standardized across brands. The process has been improved overtime as evidenced by the introduction of the NPI long-term forecast and the numerous initiatives being implemented to reduce variation in short-term forecasts. The lack of a standardized forecast translation process and limited formal feedback channels create risk management challenges for GES. Examples of this include inconsistent understanding and communication of forecast assumptions and unclear process for assessing the impact of a demand volume change on supply chain operations. It is difficult to mitigate the impact of changing demand volumes when the operational result and reason for the change are not always clearly and consistently communicated. Individuals do their best to assess the impacts of change and appropriately protect the supply chains against it. However, with the large number of new products and extensive life cycle management programs, the number of NPI brands is increasing as is scale and complexity of their supply chains. These three behaviors are more detrimental in the current state due to the resources required to complete forecast translations remaining the same, but the number of products and associated workload increasing.

There are examples of brands that do an outstanding job assessing the impact of volume changes on the supply chain and ensuring everyone has a clear understanding of the demand scenario and critical assumptions in the forecast that contribute to it. Product B is one such brand. That level of understanding and commitment results from a GSSD who is willing to put in significant time and effort to build the cross functional relationships. This includes pushing back against commercial organizations and GPPS's assumptions if a forecast change has a major impact to fully understand what caused the change. For smaller or less complex NPI, the desire or need to put in the significant additional effort to establish the necessary communication and feedback channels is limited. The lack of a formalized infrastructure makes the barrier to entry for establishing these vital communication and feedback mechanisms very high. The result is a

GES team that is not fully aware of what is causing shifts in demand and are unable to effectively mitigate the risks of demand variability due to limited information.

## 4.3 Forecast Variation Analysis

To understand the magnitude and behavior of the demand variation, a simple analysis was completed on the NPI forecasts from December 2015 to June 2018 for Products A and B. There are several types of variation that were reviewed. The first is a comparison of how much the forecast volume changes with every forecast update. Second, is reviewing variation in order volumes when different forecast versions are used for planning. Lastly, understanding how variation moves through the supply chain by observing the policy stock and manufacturing offset impacts on order volumes.

Figures 9 and 10 plot the projected demand volumes of API in the long-term forecasts with the inventory design and manufacturing offsets for formulation and packaging included. Product A was approved by the FDA and launched at the end of 2014 and Product B was first approved by the EU and launched at the end of 2010. While nearly four years separated the product launches, both products are still under the NPI designation due to on-going lifecycle management programs.

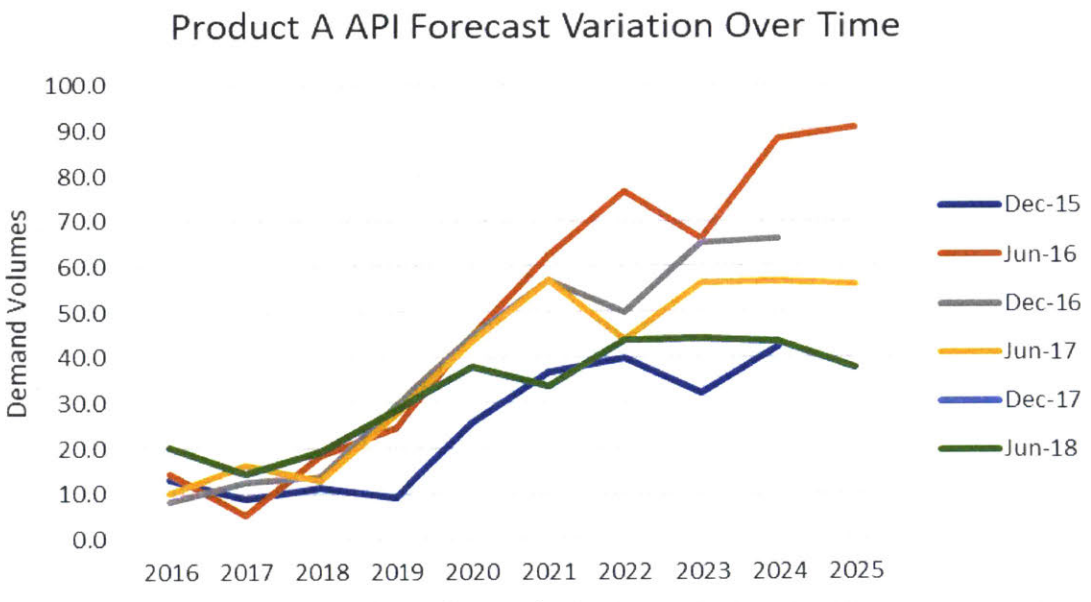


*Figure 9 - Product A API Forecast Variation*

There are a few features related to forecast version variation that can be observed in the figures. Changes in the demand, whether an increase or decrease, most often resulted in a shift up or down from the previous forecast version. The scale of variation is larger early in the product lifecycle as evidenced by the predicted demand behavior for Product A from 2016 – 2019. The peak year, defined as the year when the largest sales volume is expected, typically does not change because it is closely tied to a product coming off patent and the effects of loss of exclusivity. Large changes in expected demand volumes are not necessarily unexpected and often attributed to lifecycle management events occurring such as clinical trial readouts and new market launches. These can drastically change the future volume requirements for a product. The supply chains are typically designed to protect peak year sales volume. Product B exhibits peak year shift for API from 2023 in the December 2015 NPI forecast version to 2021 in the June

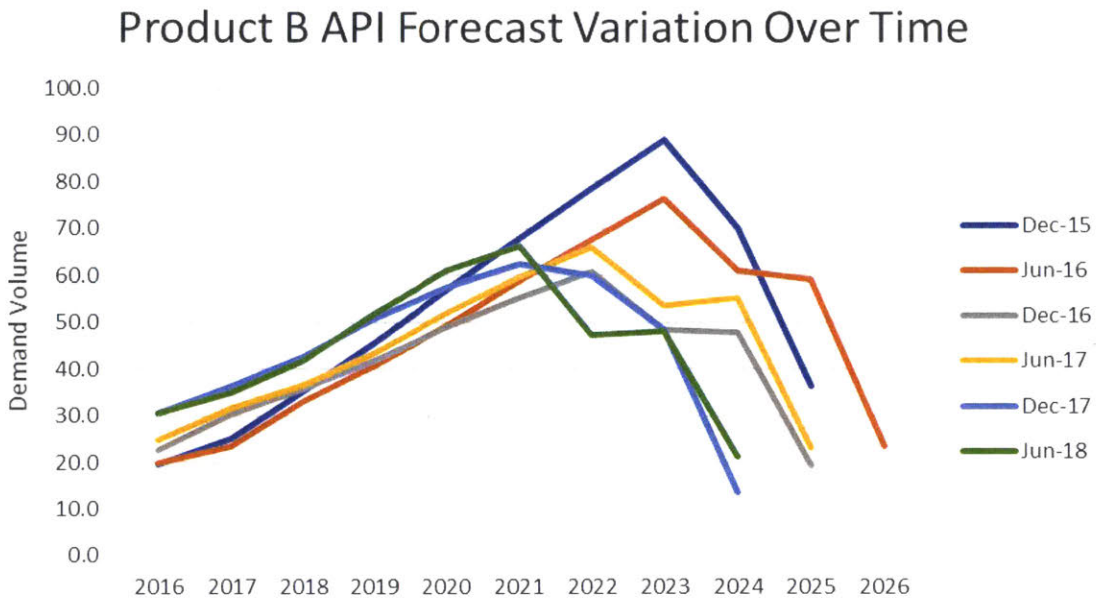


*Figure 10 - Product B API Forecast Variation*

2018 forecast version. Analysis of the brand indicates that this behavior is due to sales underperforming the long-term forecasts and an inventory build-up reducing future demand. Significant underperformance of final product sales compared to long-term forecasts is required to generate this behavior.

The final trend to highlight for forecast version variation is the oscillatory nature of the changes. Both products exhibit a phenomenon where the June forecasts are typically higher volumes than the December forecasts. The budgeting process occurs from August to December

each year and includes detailed reviews and updates to long-term plans by the brand teams. The NPI forecast process is likely influenced more by this budgeting process during the December update compared to the June update. This generates additional risk because purchase orders or supply chain decisions made using the June forecast that are not as influenced by the rigor of the budgeting process can result in a sub-optimal design if the December update subsequently reduces again.

An analysis of a single demand year was completed to assess the difference between the forecast version available when purchase orders for intermediates are placed compared to when API purchase orders are placed. The outcome is an assessment of the inventory risk associated with using different forecast versions to order material for different manufacturing stages. For the results shown in Table 5, it is assumed that there is a six-month delay from when intermediate volumes at the CMOs are fixed to when the API volumes are fixed. This directly reflects the contractual terms for the products and estimated API manufacturing time for Product A, but is only an estimate of behavior for Product B since the lead time differences between stages is more convoluted. There are three forecast translations that were done for each product. "BCP and Offset" represents the current state translation process with manufacturing offsets for formulation and packaging and the business continuity plan stock (BCP) included. "No BCP and Offset" does not include any stock builds required to be at the necessary BCP level but does include the manufacturing offsets. "No BCP and no Offset" does not include BCP volumes or manufacturing offsets. This last version is meant to capture the true variation in final demand. The each of these versions is compared to the June 2018 forecast, which is assumed to be the most representative of what the true 2019 demand will be.

*Table 5 - Example Variation in Demand by Manufacturing Stage*

| Brand | Variation in Forecast | *2019 Demand Year* | |
|---|---|---|---|
| | | API | Intermediate |
| Product A | % Variation to current forecast (BCP and Offset) | -41.10% | 56.90% |
| | % Variation to current forecast (no BCP and Offset) | -28.10% | 37.80% |
| | % Variation to current forecast (no BCP and no Offset) | -3.40% | 73.30% |
| | | | |
| Product B | % Variation to current forecast (BCP and Offset) | -10.20% | -16.40% |
| | % Variation to current forecast (no BCP and Offset) | -11.80% | -21.10% |
| | % Variation to current forecast (no BCP and no Offset) | -10% | -16.20% |

Product A is experiencing large variations in demand as shown in the "BCP and Offset" comparison which is 56.9% above the current estimate for final product demand. When API volumes were finalized, the estimated difference is -41.1%. The second version shows variation of lesser magnitude, but also bi-directional, while the third in more unidirectional change with showing only an overestimate of demand. For Product B, the variation is smaller in magnitude and only demand reductions are predicted. The more stable demand exhibited by Product B could be attributed to the product is a more mature NPI and there is more market data available for use in forecasting. The analysis identifies the potential use of different forecast versions to commit to production volumes at different manufacturing nodes as a risk of inventory buildup. It is a risk that is amplified with increased demand variability.

The final aspect of the analysis is to assess the impact of different policies and procedures on the system's behavior in reaction to demand variability. The primary focus will be on the policy stock required by the BCP. The BCP requires that certain volumes of API be held as policy stock to protect against supply disruptions for NPI and products that are of a certain level of commercial value. The volume of policy stock is defined in months of demand and calculated based on the annual estimate of demand divided by twelve. The policy stock requirements rom the BCP for Product A and Product B are shown in Table 6.

*Table 6 - Policy Stock Requirements for Business Continuity Plan*

| **BCP Plan** | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|---|---|---|---|---|---|
| *Volume of BCP Stock Required (months)* | | | | | | | | | | |
| **Product A** | 18 | 18 | 12 | 12 | 6 | 6 | 6 | 6 | 3 | 3 |
| **Product B** | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 0 |

As an oncology product and early in its lifecycle, Product A requires more policy stock than Product B, which is a cardiac product that has been on the market for several years. The use of months of demand to calculate policy stock is a widely used practice in industry and works well in stable supply chains. In highly variable demand environments, the variation in demand will also be reflected in the calculation of the policy stock. This magnitude of the impact of the variation is directly correlated to the total months of demand required by the BCP.

Figure 11 plots the net forecast and the policy stock components for two scenarios. The figure is broken down by the demand without the policy stock requirement, the net volumes of policy stock required for BCP, and the policy stock that is required to be manufactured. The two

offset scenarios considered are the current state when production volume and policy stock are offset and an alternative state when only the production volume is offset. The data in blue shows the impact of BCP when the policy stock volume in calculated with the offset demand. The data in yellow is when the policy stock volume is calculated prior to introducing the offset for formulation and packaging stages. The annual production required for API is shown in red.

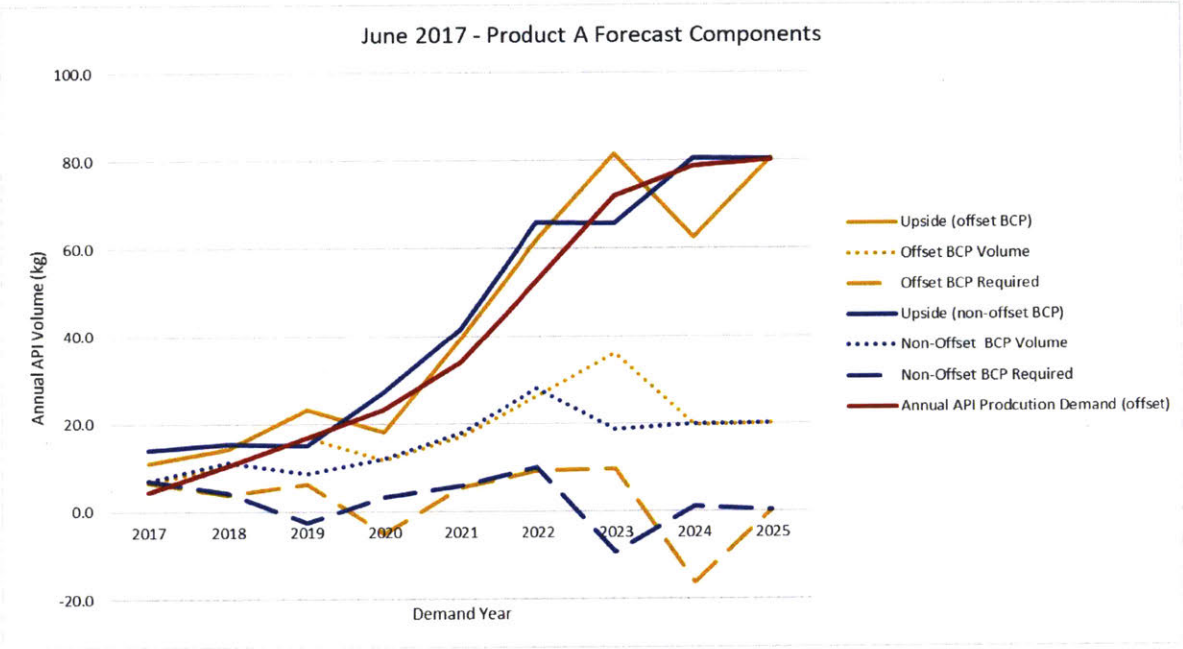


*Figure 11 - Impact of BCP on API Forecasts*

The comparison of the two different offset scenarios shows that the offset artificially increases the demand in earlier years to accommodate the policy stock requirements. A portion of a demand year's actual policy stock requirement is manufactured the year before due to the offsets. This is why the yellow data lines trend at higher volumes during the initial years when the policy stock requirements are higher. The two scenarios become balanced as demand grows and the policy stock requirements per BCP are reduced.

Most importantly, this analysis shows a clear bullwhip effect that is generated when there is a change in the required level of policy stock. From 2016 to 2017 and 2018 to 2019, there is a reduction in the required number of months of policy stock. This results in a reduction in the policy stock volume required to be in stock. In Figure 11, where the lines drop below zero, it shows that the annual demand is artificially reduced because some of the policy stock will be converted to working stock for formulation and packaging. This is a direct source of variation in demand that the supply chain observes and experiences. It is entirely generated by the processes and information AstraZeneca chooses to share with the supply base and is not generated by the actual variations in final product forecasts. The scale of the impact is shown in Figure 12.

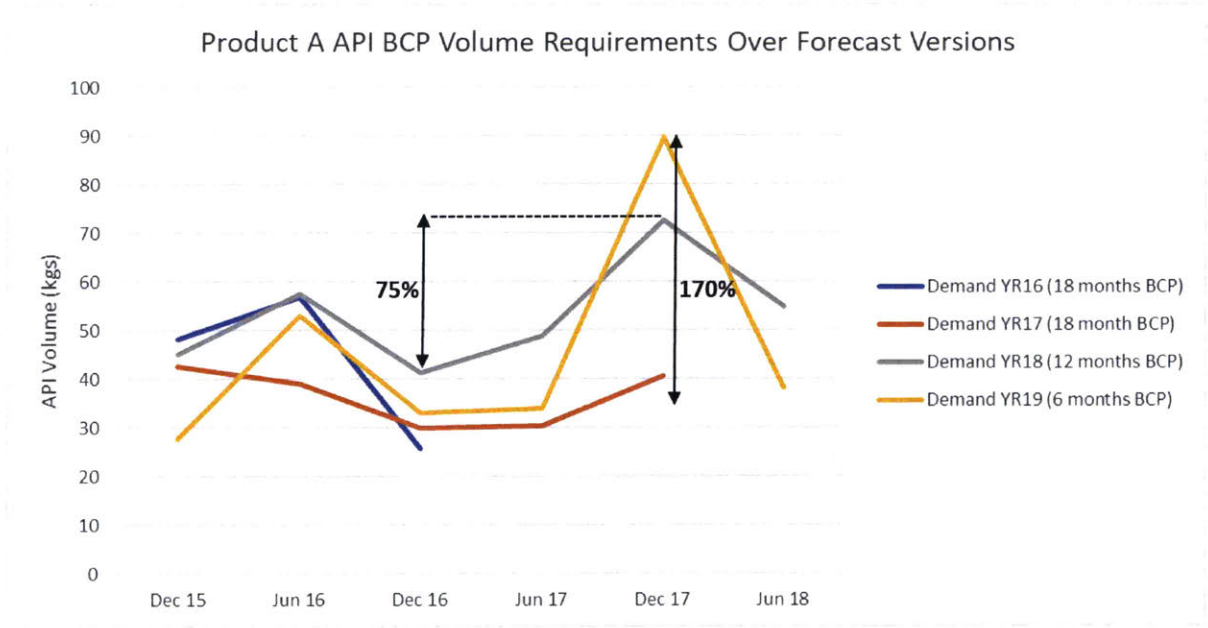


*Figure 12 - Impact of BCP on API Forecasted Volumes*

Figure 12 shows how the required volume of policy stock varies for a given demand year with forecast versions. In years where the BCP requires twelve months or more of policy stock, the inventory risk associated with the variation in demand is doubled. The volume impact can be as large as an 170% increase in volume required as evidenced by the 2019 demand year forecast volumes.

While uncertainty in forecasts and the actual methods to develop the final product forecast do contribute to demand variability, this source of variation is to be expected. It comes from the inherent volatility of pharmaceutical products around launch and the impact on on-going clinical trials and new market launches. However, there are supply chain design, operation and

procedural methods that amplify this variation, increasing the risk of inventory performance issues. The monthly BCP stock calculation method, segmented supply chain and limited information flow on the forecasts all increase the impact of demand variability. This impact will be addressed in the impact assessment directly and potential mitigation strategies will be identified in sections 6.1 – 6.2.

## 4.4 Supplier Relationships

The final functional area in the current state analysis is supplier relationships. The findings in this section are all based on interviews with employees at AstraZeneca and suppliers A, B and C. The suppliers all expressed that the working relationship with AstraZeneca was positive and they understood they were critical to AstraZeneca's operation. However, they would not describe the relationship as strategic when compared to relationships with their other customers. If partnership with these suppliers is the vision for the future of supply chain operations at AstraZeneca, changes to the system to improve behaviors and transparency that are more reflective of a partnership instead of a transactional relationship are required. A summary of supplier interviews including relevant company information and the customer relationship are included in Table 7.

*Table 7 - Supplier Overview*

| Supplier | Company Information | Relationship Notes |
|---|---|---|
| *Supplier A* | - Pharmaceutical manufacturing is one business unit within a large, publicly traded company<br>- Customers include small to large pharmaceutical firms<br>- Outstanding technical and quality reputation<br>- Multi-facility manufacturing site with varied capabilities and reactor sizes. Largest capacity of three suppliers<br>- Commercially focused and skilled negotiator | - Rebuilding trust on both sides due to some contract issues in the past<br>- Supplier is extremely cost and business focused<br>- Only transparent at the working level when directly asked on a specific topic<br>- Less reliant on AZ business compared to other CMOs due to scale of their operation<br>- Desire to expand offerings for AZ and work more closely<br>- Quality and technical capability are never in doubt with this supplier<br>- Seen as commercially inflexible and the business function has the most organization power<br>- Have a reputation for charging for every item, regardless of scale, that is outside of the contract |
| *Supplier B* | - Privately held, mid-size CMO<br>- Primary business is API manufacturing. Pharmaceutical is a majority of customers, with some specialty chemical<br>- AstraZeneca is a major customer, but favor working with mid-size firms. Have customers of all sizes<br>- Emphasis more on technical excellence than commercial focus. Significant number of PhD's in all types of roles.<br>- Small company culture and feel<br>- Risk adverse when it comes to investing in facility and operational upgrades | - Transparency varies depending on function and level within the company. The technical teams have a very strong relationship<br>- AZ is a demanding customer, but supplier will try everything feasible to meet needs of customer<br>- Relationship requires a lot of hands-on time by supplier<br>- Build capacity based on long-term forecasts, so accuracy is critical<br>- Limited resources mean strategic decisions about supply chain ownership may not benefit them<br>- AZ team is strong, but can dominate discussions |
| *Supplier C* | - Spin-off of a large chemical manufacturing company, so comparatively new as a supplier<br>- Most customers are small/mid-size firms<br>- Full-service pharmaceutical CMO, including generic manufacturing<br>- Strength in providing clinical supply for other customers<br>- Proactive in investing in capabilities and capacity to meet customer's future needs | - AstraZeneca is one of two major customers<br>- Expanding operations in both capacity and capabilities<br>- Value relationships highly and they are the most open across all functions with AstraZeneca<br>- Most transparent at the senior leader level<br>- Trying to build business, so invest heavily in relationship with AZ<br>- Operationally and commercially creative to better meet the needs of customers<br>- Viewed as a very flexible supplier by GES team |

Each of the suppliers approach their relationship with AstraZeneca and operational strategies slightly differently due to different business strategies and company positioning at each of the suppliers. However, all agree that working with large pharmaceutical companies has a different set of challenges compared to working with small and mid-size companies. Large pharmaceutical companies typically tech transfer products that are well developed and have

limited technical and regulatory challenges. For smaller customers, technical expertise and experience around process development are necessary. The CMOs must invest more time and effort into the relationships to maintain current business and have new business opportunities with larger companies. These customers will drive hard to get the lowest possible cost, while expecting the relationship side of the business for free or little additional cost. The idea of "having the best of both worlds" for companies like AstraZeneca erodes trust and willingness to be flexible at the CMOs.

One individual reflected that it will be very hard for "big pharma" to develop true partnerships with CMOs because it requires a major shift in culture and behavior on both sides. The discussions highlight several behaviors and practices that make it difficult to work with AstraZeneca. While these were mentioned in reference to AstraZeneca, two of the three suppliers indicated that the behavior is similar at other major pharmaceutical companies they work with.

- **Cost of the product** is the most important factor in contract negotiations. AstraZeneca may express that they want increased flexibility and creative commercial or operational solutions, but when it comes to negotiating the final supply agreement, cost seems to always be the most important factor. Contract negotiations typically include the supplier manager, lawyers, finance and individuals from the contracts organization. This is a reinforcing cycle that results in the contracts having the minimum volume commitments, long lead times and large batch sizes since that is the lowest cost operating model at the CMO.
- **Lack of transparency in forecasts** prevents the CMOs from understanding the risks adequately and can result in them being surprised by deviations from the previous forecast version. The rationale for major shifts, underlying assumptions and probability of the forecast volume occurring are not well understood. In addition, the process AstraZeneca uses to determine the API demand from the final product demand is not well understood. Several suppliers mentioned that they try to estimate the API demand based on the product sales and market data and it does not always trend with the forecasts they receive from AstraZenca. There can be clear indications of product growth in sales figures and investor presentations, but they could see

decline API demand. The perceived inconsistencies degrade trust and fuel the bullwhip effect.

- The **Request for Proposal (RFP) process** reduces trust with the CMOs and is a source for frustration. Two of the suppliers felt that if they were a strategic supplier of AstraZeneca, the same level of administrative rigor should not be required as other non-strategic suppliers. They also do not always understand the exact needs and the strategic relevance of a single RFP to be able to put in a competitive bid. The suppliers are happy with the results of the RFPs recently and the amount of AstraZeneca work they have been awarded. However, there are opportunities to improve the RFP process for strategic suppliers and improve transparency of future needs so the suppliers can be more proactive and anticipate the needs of AstraZeneca. This could result in a supply base that is better able to achieve AstraZeneca's capacity and technical needs on shorter time lines because proactive behavior would be incentivized.

All of these issues come down to the lack of trust and transparency in the relationship and the limited information flow between both parties. While several individuals expressed the idea of a win-win relationship being infeasible, steps toward a partnership model are desired by all parties. The suppliers believe it will help them be more competitive and also help stabilize their operations through increased transparency and the ability to better anticipate and react to the changing business needs of the brands to provide the highest value to patients. Such a relationship would cost money and require more investment of time and resources, not just funds, by AstraZeneca. If a strategic partnership model is a requirement to create the supply chain of the future as part of the GES 2025 strategy and vision, the first step towards increasing transparency and building trust needs to be taken by AstraZeneca. The lack of confidence in AstraZeneca following through with partnership discussions needs to be overcome. This will make the company vulnerable, but is a necessary trust building step that would signal to the suppliers that the company is serious about partnerships and it is not just "talk".

# 5 Simulation Methodology

The conceptual model of the simulation is based on taking forecast data and a supply chain design to create an inventory flow model. The block diagram in Figure 13 shows the general structure of the simulation needed to achieve the research goal. There are two sub-systems that make up the model. A push system that models the drug substance procurement and manufacturing process and a pull system for the drug product system, which includes formulation and packaging. The integration of these two systems occurs at the API stock, which is the current point when the shift from using the long-term forecast to short-term forecast in manufacturing planning occurs. The line that separates the push system from the pull system can be moved further upstream through reduction in overall lead times. This would result in different manufacturing nodes being able to use the short-term forecast.

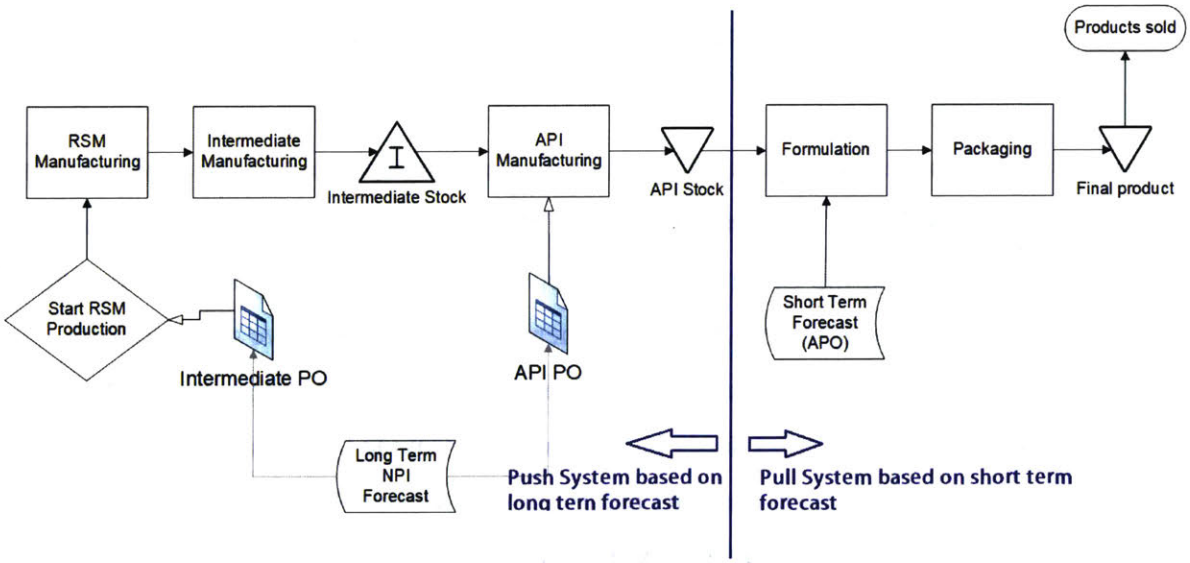


*Figure 13 - Simulation Conceptual Model*

For the purpose of this research, the focus is on developing a simulation for the push system only. Due to data availability and aggregation challenges with the short-term forecast data, further development of the forecast translation model was prioritized over developing the pull system model.

The model is designed to be a high-level representation of a typical supply chain that GES manages. This allows for ease of customization across brands. The input parameters are the

forecast data, supply chain lead times, manufacturing parameters and contractual framework for ordering APIs and Intermediates. The output is the expected flow of materials through the supply chain and inventory stock pocket volume and dollar measurements over time.

## 5.1 Simulation Strategy

The supply chain and manufacturing operation being modeled has two distinct parts – the forecast translation and the execution of the supply chain design. Ease of use and broad application are the most important design attributes. Simulation and coding are new concepts for many individuals in the organization. Developing a model and simulation tool that is easy to use, customize and understand is critical for future adoption. Therefore, accuracy and detailed representation was traded-off in favor of these attributes. While it was feasible to create a model that is more complex and can accurately measure inventory performance for a specific brand, it would not be possible to successfully transfer the tool, nor would it be repeatable for other brands due to limited technical experience with developing these types of models. These are the driving design factors.

The two models have different analytic and modeling requirements that require segmentation of the simulation. The forecast translation process is primarily an analytic activity where computing power and looping logic are important for performance. The supply chain execution is about visualization and ease of understanding material movements. MATLAB is used to simulate the forecast translation process. It was selected because of its seamless integration with Microsoft Excel, computational power and looping logic. MATLAB licenses are available to all AstraZeneca employees, so additional licenses are not required to use the tool. FlexSim was selected as the supply chain simulation tool because of the high level of functionality of the lite software package, drag and drop approach to developing models and ease of integration with excel.

The overall tool is Excel centered, using a workbook as the primary data collection and storage location. The MATLAB scripts for forecast translation interface with a sheet in excel and then write the purchase order schedule back to Excel. FlexSim then looks for the purchase order schedule in Excel and pulls this data into the simulation to execute the material movements. Inventory performance is observed in FlexSim and measured over time. Static analysis of inventory performance can be done independently with the data that is generated by MATLAB.

The Excel centered approach is intentional because it is a program that most employees within GES are proficient in and capable of accomplishing detailed analysis within the software.

Figure 14 shows the software structure the tool utilizes in more detail. The excel file is where the user primarily interfaces with the tool. In MATLAB, the user is only required to open the main script and click "play". It is similar for FlexSim with the only addition being any data tracking or metrics need to be toggled. The software is intuitive, and it is reasonable to assume that any GES employee would be able to configure the simulation package to track the data that is of most interest to them after completing basic tutorials.

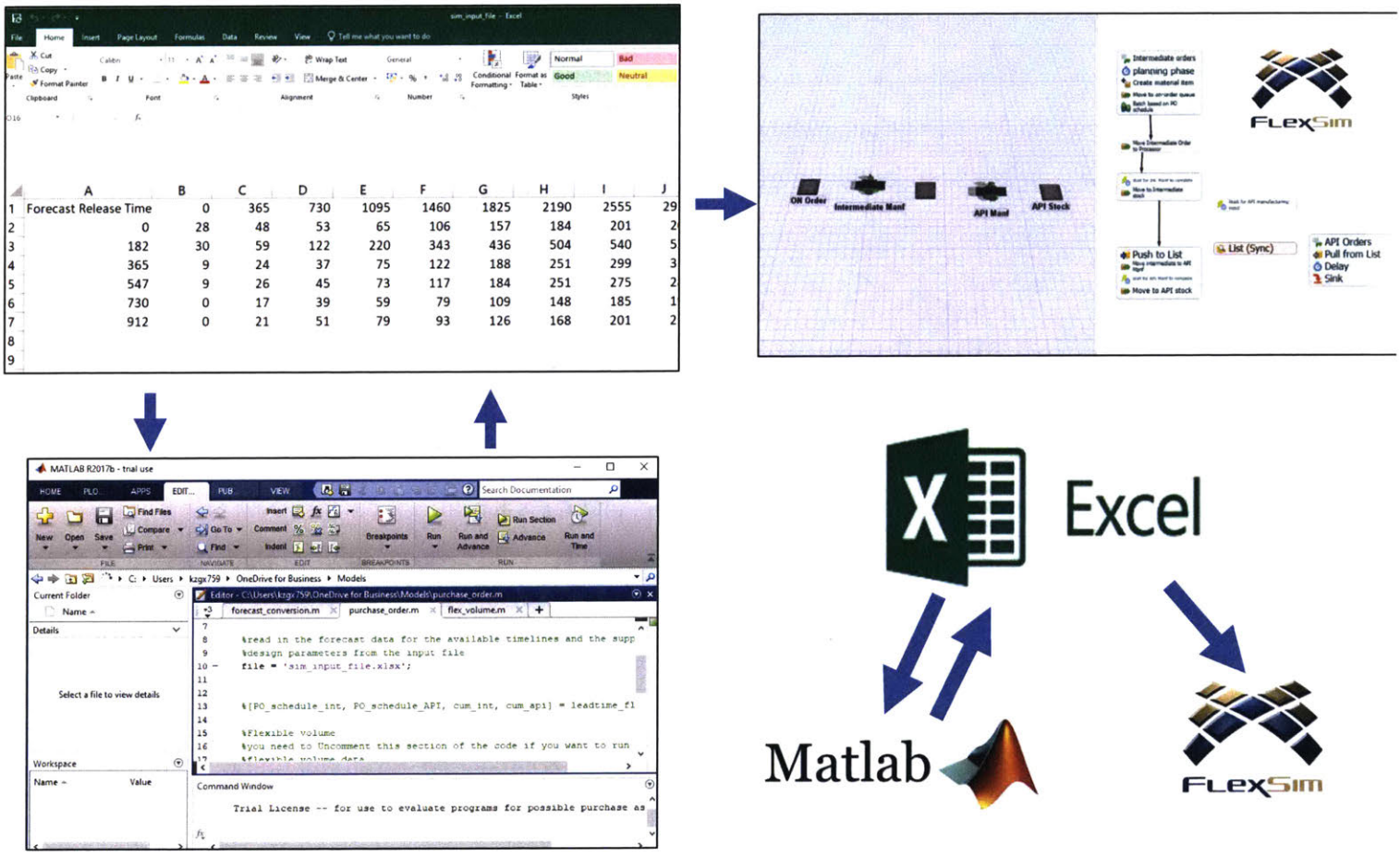


*Figure 14 - Software Strategy for Simulation Tool*

While this simulation strategy is not the most efficient or accurate, it is easy to use, understand and transfer to most brands managed by GES. The user is expected to interact primarily with Excel, which is familiar, and the forecast data inputs already exist in Excel files. In the future, this strategy can be expanded to accomplish more detailed analysis once the

technical capability around coding and simulation has been built up within GES and the larger operations organization within AstraZeneca.

## 5.2 Forecast Translation Process

A standard method for translating the SMU forecasts to API forecast was defined based on a combination of the processes used by asset planners. For the simulation, the translation process stops at API forecast volume and the common unit is kilograms of API through all stages. The conversions from API to intermediate and then RSMs are not considered because the primary goal of the simulation is to understand the inventory behavior of API stock with changing demand forecasts. The additional layer of detail from converting materials through yields and recipes for upstream stages is not required to achieve the goal.

The forecast data input for the simulation is a matrix of forecast versions and demand years. A screen shot from the input file is shown in Figure 15. The base data is the GPPS flat files for each forecast released through the NPI process. The flat file is an extensive table of all the markets, indications, formulation and use types for the next ten years that are generated through the forecasting process. This file must be aggregated to find the total volume of each formulation per demand year. The aggregation process is accomplished in an Excel sheet with the output being the forecast matrix. In future, this process could be automated using MATLAB, but initial translations were completed in Excel because that matches the general current state process used by asset planners.

| | Demand Year | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Forecast Release Time** | **0** | **365** | **730** | **1095** | **1460** | **1825** | **2190** | **2555** | **2920** | **3285** |
| **0** | 28 | 48 | 53 | 65 | 106 | 157 | 184 | 201 | 209 | 35 |
| **182** | 30 | 59 | 122 | 220 | 343 | 436 | 504 | 540 | 553 | 311 |
| **365** | 9 | 24 | 37 | 75 | 122 | 188 | 251 | 299 | 319 | 327 |
| **547** | 9 | 26 | 45 | 73 | 117 | 184 | 251 | 275 | 280 | 282 |
| **730** | 0 | 17 | 39 | 59 | 79 | 109 | 148 | 185 | 195 | 193 |
| **912** | 0 | 21 | 51 | 79 | 93 | 126 | 168 | 201 | 215 | 219 |

*Figure 15 - Example Forecast Matrix for Simulation Input*

The first calculation step is to aggregate the total SMU by formulation type. $D_{form}$ represents the aggregate final product demand across all markets, indications and use types for each product formulation. $D_{form}$ is calculated through the summation of the raw SMU data, $d$, where $i$ is the number of markets, $j$ is the number of indications and $k$ is the number of use types. The output is a matrix of the aggregate SMU volumes by formulation type for all 10 forecasted demand years.

$$D_{form} = \sum_i \sum_j \sum_k [d_{ijk}] \tag{1}$$

The $D_{form}$ must be converted to API based on the formulation type. It is composed of values $D_{form,m}^{year\ n}$ at each index location and represents the aggregate demand where $n$ is the forecast demand year from 1 to 10 and $m$ is the number of formulation types. The chemical recipe defines the number of kilograms of API per SMU and is represented by a diagonal matrix with $x_m$ being the conversion factor for each formulation type. A matrix multiplication step converts $D_{form}$ to aggregate API demand by formulation type, $D$, with dimensions $n$ x $m$.

$$D = \begin{bmatrix} D_{form,1}^{year\ 1} & \cdots & D_{form,m}^{year\ 1} \\ \vdots & & \\ D_{form,1}^{year\ n} & \cdots & D_{form,m}^{year\ n} \end{bmatrix} \begin{bmatrix} x_1 & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & x_m \end{bmatrix} \tag{2}$$

The supply chain design is introduced after the aggregation steps by offsetting demand by the drug product lead time. It is key that the demand is still split by formulation type to allow for different lead times based on formulation type. The offset is defined by the lead time in months for formulation ($t_{form,m}$) and packaging($t_{pack,m}$) and represented as $k_m$.

$$k_m = t_{pack,m} + t_{form,m} \tag{3}$$

$$D'_{m,1} = D_{m,1} + D_{m,2} \cdot {}^{k_m}/_{12} \qquad \text{(for n = 1)} \tag{4}$$

$$D'_{m,n} = D_{m,n}\left(1 - {}^{k_m}/_{12}\right) + D_{m,n+1} \cdot {}^{k_m}/_{12} \quad \text{(for n} \geq 2) \tag{5}$$

With all of the offsets included, the total API demand can be aggregated within a demand year and is represented by $D_{net}$.

$$D_{net} = \sum_n D'_n \tag{6}$$

$D_{net}$ is the API forecast vector with dimensions 1 x 10 and contains the total API required for each of the 10 years forecasted for the final product state. The final factor that needs to be applied is the addition of policy stock if additional material is required. $PS_{build}$ is the additional amount of API required to be manufactured to achieve the policy stock volume requirements. It is calculated using $PS_n$, volume of policy stock on hand, and $b_n$, the months of policy stock

required per BCP. $D_{final,n}$ is the net amount of API required adjusted for any increase or decrease in policy stock volumes.

$$PS_{build,n} = D_{net,n} \cdot b_n/12 - PS_n \tag{7}$$

$$D_{final,n} = D_{net,n} + PS_{build,n} \tag{8}$$

This calculation captures the ability of the policy stock addition to either increase or decrease the final API demand that is used for the drug product manufactures. $PS_{build}$ is negative when the policy stock requirement is reduced and some of the stock is converted to production stock. The result is a vector for a specific GPPS NPI forecast version, $D_{final}$, where each of the indices is the final forecasted demand for the 10 years covered by the forecast horizon. For representative purposes only, the annual demand volumes are represented by $a_1$ to $a_{10}$.

$$D_{final} = [a_1 \quad a_2 \quad a_3 \quad a_4 \quad a_5 \quad a_6 \quad a_7 \quad a_8 \quad a_9 \quad a_{10}] \tag{9}$$

The series of calculation steps in the translation process are repeated for every forecast version. The combination of the $D_{final}$ vectors from every available forecast version comprises the forecast matrix shown in Figure 14. The number of rows in that matrix grow with the number of forecasts released.

The translation process occurs in an excel sheet with the output being the forecast matrix. This matrix and the supply chain design parameters, including all the stage lead times, are input into a separate excel sheet in the same workbook, sim_input.xls, which is the read/write interface with MATLAB and the read interface for FlexSim. A MATLAB execution script is the main script that reads the forecast matrix, runs functions to generate the purchase order schedules and write back to the input file. The user toggles a series of functions that execute the mathematical operations depending on the type of analysis the user wants to do. There are two types of analysis in the simulation models – lead time definition or a flexible volume model. The lead time definition is meant for iterative supply chain design and addresses the research objective of being able to estimate the financial impact of lead time improvements as measured by inventory levels. The leadtime_flex.m script executes the following steps to translate the inputs into a purchase order schedule for the FlexSim model.

(1) Converts the forecast matrix data into numerical data and assigns the supply chain design parameters to each of their respective variables for use in the script.
(2) Checks the lead times against the manufacturing times in the supply chain design to determine that the RSM leadtimes are within the Intermediate planning horizon and that the API leadtime is at least as long as the manufacturing time. If either of these are not true, the script prints an error message and terminates to indicate there is a conflict in the supply chain design.
(3) Defines the offset times for ordering intermediates and API based on the supply chain design parameters.
(4) Starting with API, define initial conditions for all variables and determine which demand year is the first year that purchase orders could be generated on and set as the initial condition for year.
(5) Looping through time, the script defines the time where purchase orders need to be made, searches the forecast matrix based on tracking indices, and then pulls the volume of material to be ordered. This is stored in an output matrix. Once the end of the defined time horizon is reached, the loop is exited and the output matrix is the data of interest
(6) Repeat steps 4 and 5 for intermediates.
(7) Returns the purchase order schedule for intermediates and API and vectors for the cumulative volume ordered for each demand year.

The alternative function that can be run in the execution script is flex_volume.m. The purpose of this function is to assess the inventory impact of different commercial models. This commercial arrangement allows for the gradual build-up to the final commitment volume for a given demand year over defined intervals instead of a single point in time where the volume of material is committed. This model requires additional inputs in the sim_input.xlx file for the percentage of the demand that is committed to at each of the lead time milestones. An example is shown in Table 8 where at 24 months prior to material receival, AstraZeneca commits to 50% of the forecasted demand, 6 months later commits to 75% of the forecasted demand and 12 months prior to material need, 100% of the demand volume is committed to the CMO. This allows for the

*Table 8 - Example Commercial Framework*

| Phase | Lead Time (months) | Percentage Commitment |
|---|---|---|
| A | 24 | 50% |
| B | 18 | 75% |
| C | 12 | 100% |

production volume to be gradually built up and adjust to updated forecasts. In addition, it does not allow for volume reductions. The supplier only needs to deal with variation due to increases in demand and AstraZeneca would have the option to not order any additional volume of material at the B and C ordering points.

This function uses the same search methodology as the leadtime_flex.m function with additional iterations for the B and C orders. Figure 16 shows the computational framework for defining the B and C purchase order volumes. Two output matrices are the purchase order schedule and a cumulative material tracker. These are utilized to capture the data and allow it to be referenced within the function. The A ordering computation is exactly the same process as the leadtime_flex.m function with the defined volume reduction factor added. B and C introduce complexity in the computation because the current material on-order must be known to determine how much should be ordered or if no additional material should be ordered.

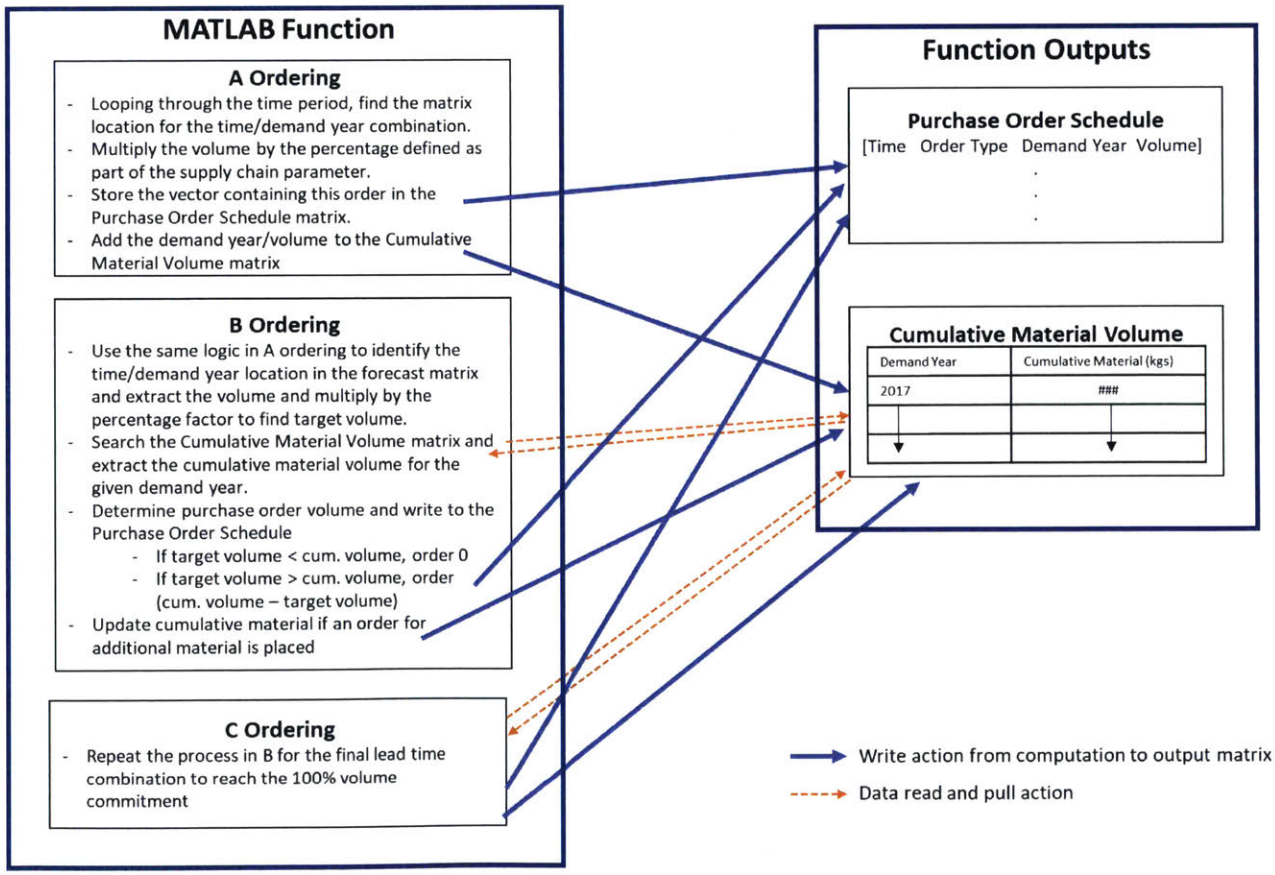


*Figure 16 - Flexible Volume Ordering Computational Framework*

There are several other functions that were written to complete various parts of the computations in the leadtime_flex.m and flex_volume.m functions to simplify the code. The nature of these functions is captured in the explanation of the two primary functions. The output data is formatted like a schedule. Examples are shown in Tables 9 and 10.

*Table 10 - Example Purchase Order Schedule Output*

| Time(days) | Order Lead Time(days) | Order Qty(kg) | Demand Year |
|---|---|---|---|
| 0 | B | 46.5 | 365 |
| 182 | C | 0 | 365 |
| 182 | A | 61 | 730 |
| 365 | B | 0 | 730 |
| 547 | A | 0 | 730 |
| 547 | C | 36.5 | 1095 |
| 730 | B | 7.75 | 1095 |
| 912 | A | 34.75 | 1095 |
| 912 | C | 46.5 | 1460 |

*Table 9 - Example Cumulative API Output*

| Release Time(days) | Name | Quantity | Volume | Demand Year |
|---|---|---|---|---|
| 548 | 0 | 1 | 61 | 730 |
| 913 | 0 | 1 | 44.25 | 1095 |
| 1278 | 0 | 1 | 81.25 | 1460 |

## 5.3 FlexSim

The FlexSim model is a two-stage manufacturing supply chain in which there is a virtual stock location and two physical stock locations. The drug substance manufacturing process is a three-stage manufacturing supply chain, split into RSM, intermediate and API manufacturing conversion stages. For the purpose of the simulation, RSM and intermediates were combined into a single stage because the RSM lead times are most commonly within the planning window for intermediate manufacturing. The model can be expanded to include a third stage if required, but for the initial intended use of the simulation, it is a level of detail that is not required to achieve the analysis goals. The 3D model framework is shown in Figure 17.

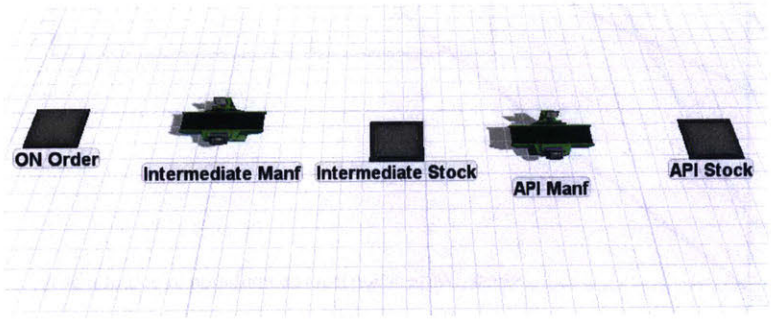


*Figure 17 - FlexSim 3D Model Structure*

The manufacturing stages appear as the conveyor belts and the stock locations are the squares. "ON Order" is the virtual stock location and represents the volume of material that has been committed to by AstraZeneca, but the manufacturing has not begun yet. When a purchase order for intermediates is placed, the volume is loaded into this stock location. Based on the defined manufacturing stage times, the

"Intermediate Manf" stage pulls a batch of material from the "ON Order" stock and pushes it into the "Intermediate Stock" location.

The "API manf" stage is executed slightly differently to capture any differences in forecast volumes from when intermediate purchase orders are placed compared to API orders. The API purchase order volumes are loaded into a list at the start of the simulation run. When an API campaign start is triggered based on the supply chain design parameters, it searches the list to determine how much of the intermediate stock should be pulled into the manufacturing stage. It then simulates the manufacturing stage and pushes the stock into the "API Stock" location. If there is not enough intermediate stock to cover the API campaign, the simulation flashes red at that point in time.

All of the logic to execute the simulation is built within the process flow in FlexSim. Process flows can be standalone operations or complementary to a 3D model. This simulation was designed to use process flows together with a 3D model to simulate the supply chain behavior and visualize stock movement. The process flow is shown in Figure 18. The Excel integration points are identified. This is where the purchase order schedules calculated in the MATLAB model are pulled into the simulation model. Time delays are introduced to delay the material from entering the initial manufacturing phase to model the planning periods. The "create material item" action is the integration point between the process flow and the 3D model. This creates the boxes that will flow through the supply chain in the 3D model. They are batched to meet the annual demand volume to replicate the annual campaign strategy used by drug substance manufacturers.

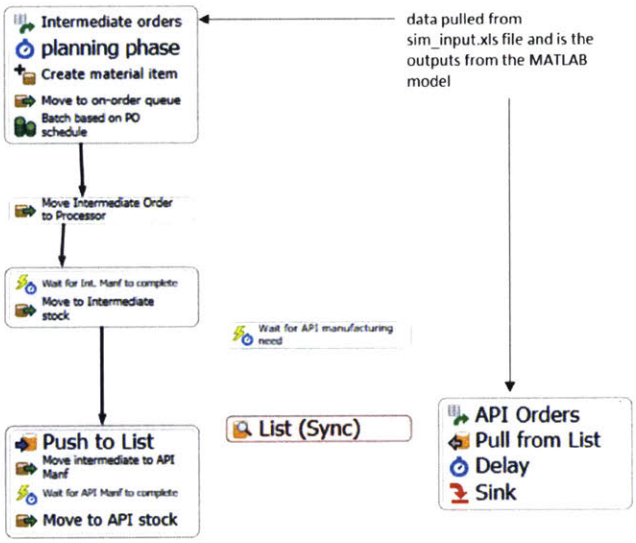


*Figure 18 - Simulation Process Flow*

The process flow creates tokens that each represent 1-kg of material. When the material is batched, it moves through the process flow and 3D model as a single item with a value equivalent to the sum of the tokens combined to make the batch. When the batch enters a stock

location, it is unbatched into the list object to allow for the material to be re-batched when entering the API phase. This batching behavior is mirrored in the 3D model.

## 5.4 Simulation Output

This simulation is a powerful tool to understand how the supply chain design and forecasts interact from the perspective of inventory performance. The run times for the MATLAB scripts averaged 30 seconds and FlexSim model is 1-3 minutes depending on the simulation speed selected. This allows for the tool to be effective for quick iterations and readily be customized to different brands' supply chains or specific design parameters. The combination of the MATLAB computations integrated with FlexSim provides visualization of the stock movement over the simulation period. Figure 19 shows the 3D model, process flow and an example data output. As an iterative design tool, this allows the user to very quickly understand the location of bottlenecks, inventory build-up risks and general material flow that was previously difficult to understand through Excel analysis. It will be used to estimate the inventory value of lead time reductions in the impact assessment and test the potential benefits of alternative commercial product in brand specific applications.

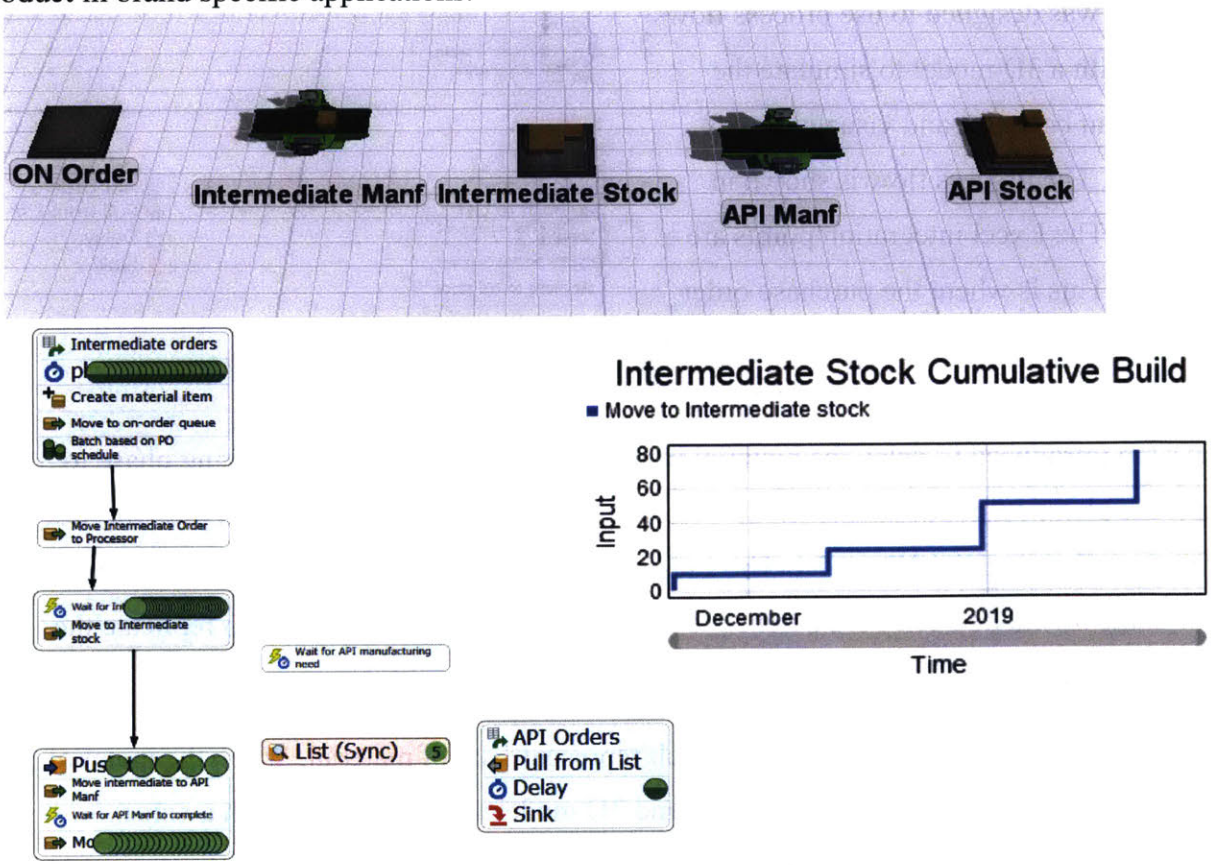


*Figure 19 - FlexSim Visualization Examples*

# 6 Impact Assessment Results

The current state analysis identified several areas of the supply chain and manufacturing operations that are directly impacted by variation in long-term demand forecasts. The purpose of the impact assessment is to identify the non-financial and financial impacts that result from demand variation in long-term forecasts to fulfil one of the research objectives. This section will define what an impact is for the purpose of this research and identify the impacts based on the current state analysis. The impacts are focused on the external supply chain, but the causes may occur on other parts of the system that do not fall under the responsibilities or processes within GES. Many of these impacts are evidence of the bullwhip effect in the supply chains for these two NPIs.

Demand variability for the context of this research has been defined as the variation in API demand in subsequent long-term forecasts for a given product. The problem statement defined two types of impacts – financial and non-financial – as an attempt to understand a broad spectrum of potential impacts that are feasible to mitigate. For the purpose of this research, a financial impact is defined as one that has a directly measurable impact on the product inventory at the defined inventory stock pockets. This definition is intentionally restrictive because there is an established method for measuring the financial value of inventory. Inventory performance is a widely understood metric across multiple organizations within AstraZeneca. The current state analysis highlights inventory performance as a high profile improvement opportunity and there is a need for a simple way to assess improvements or strategic changes.

There are other financial impacts such as write-offs, non-contract spend and inventory holding costs. However, these are not able to be consistently measured across the different brands and there is limited data available to support analysis. Non-financial impacts are defined as any activity, behavior or process that is negatively impacted by demand variability but cannot be measured directly through inventory. These can be items like supplier relationships, system complexity, difficult contracts and work environment. Non-Financial impacts resulting from variation in demand have the greatest breadth of impact but are difficult to isolate and measure due to the ambiguity of measurement methods and ability to attribute it to a single source. Examples of this type of impact include sub-optimal supply contracts, trust, supplier relationships and complexity.

## 6.1 Financial Impacts

There are three measurable financial impacts that the analysis uncovered resulting from forecast demand variability for NPI. The BCP policy stock methodology, segmentation of supply nodes and a disconnect between the NPI long-term forecast and short-term forecasts all amplify the financial risk associated with demand variation in forecasts. These three procedural items introduce an amplified impact of demand variation into the supply chain system and can be mitigated through policy and process changes. While there are other financial impacts, these have the potential for the greatest risk reduction and also would be feasible to address within a year.

The calculation of policy stock levels per the BCP requires an average monthly demand to be calculated and stock levels defined in number of months. This is a sound and standard process for calculating policy and safety stock levels that is well proven across multiple industries. However, for NPI where the environment is expected to have highly variable demand due to the sensitivity to clinical trial read-outs and regulatory approvals, using this standard process introduces two separate impacts resulting from variation. Any variation in forecasted demand has a major financial impact early in an NPI's life when the BCP requires 12 – 18 months of policy stock. This impact is directional because assessment showed it was only a measurable financial risk if a product is performing below forecasted levels. If sales exceed the forecast, the policy stock can be utilized to make up the difference in required product. However, if the actuals are 10% less than the forecasted demand, this means there is an additional 20% of stock between the product stock available and policy stock that was required. For product A, the estimated change in stock requirements due to demand forecast variation is between 75% to 170% change in volume requirements for the example demand years shown in Figure 12 from section 4.3.

The segmentation of supply nodes requires a separate contract per node which means there are separate lead times and purchase orders for materials in upstream nodes compared to downstream nodes. If the difference in the lead times for purchase orders is greater than six months, different NPI forecasts will be utilized to determine the volume of material to be ordered. Figure 20 measured the expected difference in ordering volumes for intermediates and APIs using the forecast data and current supply chain system. The difference in volumes equates to an inventory risk. It has the potential to result in under or over-ordering materials unless an

individual intervenes and manually adjusts an order or works with the supplier to change the volume outside of the contract terms. The percentage differences displayed equate to millions of dollars of inventory risk and are calculated using standard material costs for the stage materials. While in practice manual interventions can be taken to adjust orders or exercise contract options to make-up for any differences, the current system of forecast translation, supply chain design and execution generates this risk.

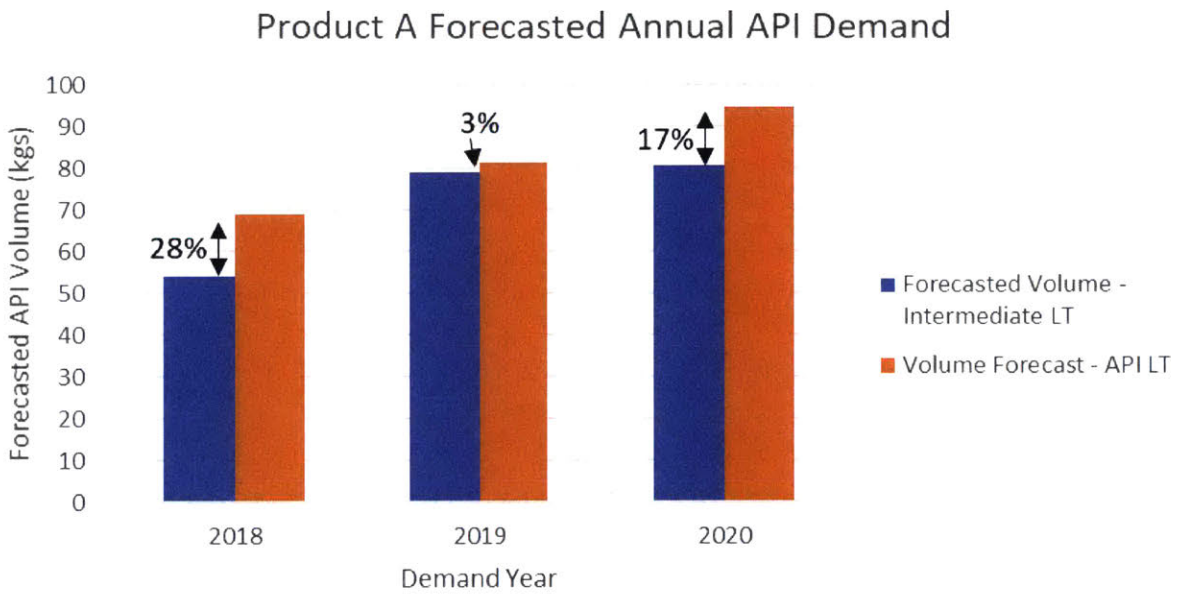


*Figure 20 - Estimate of Order Volume Difference Due to Leadtime Mismatch*

The final financial impact that results from demand forecast variability is also related to different forecasts being using to execute manufacturing at different stages. Unlike the last impact, which results from using different forecast versions being utilized, this is related to using two different processes to generate the forecasts being used. Manufacturing planning for formulation and packaging can be executed utilizing the short-term forecasts for all products, regardless of their NPI status, because the planning lead times are within the forecasting horizon. In most cases, all manufacturing upstream of formulation utilizes the NPI long-term forecast if it is in that category. It is necessary to utilize the different forecasting methods and forecast versions due to the multistage nature of pharmaceutical manufacturing and lead time restrictions. Comparing the forecasted volumes for a given demand year based on the specific forecast method used or version available allows for the value of reducing the API lead times to be financially measured. This is one method for estimated the impact of the bullwhip effect.

Utilizing the simulation tool, an estimate of the expected API volumes for Product A that would be ordered was generated based on the forecast for three different lead times and compares that to the current short-term demand forecast. Both the high-side and base-case forecast volumes were plotted based on the simulation. The short-term (ESF) forecast is plotted with the net lead time on the x-axis and forecasted volumes on the y-axis. In Figure 21, the supply chain system utilizes the current state drug product manufacturing lead times. The process was repeated with a reduction in formulation times so both formulation types for Product A have a three-month lead time. This is shown in Figure 22.

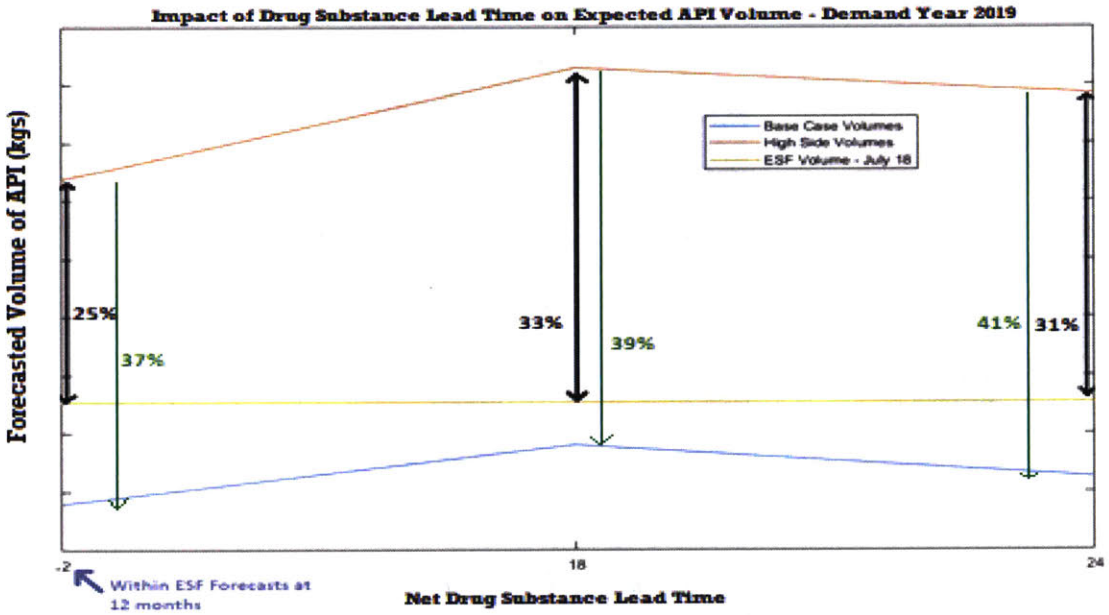


*Figure 22 - Impact of Using Different Forecast Methods - 1*

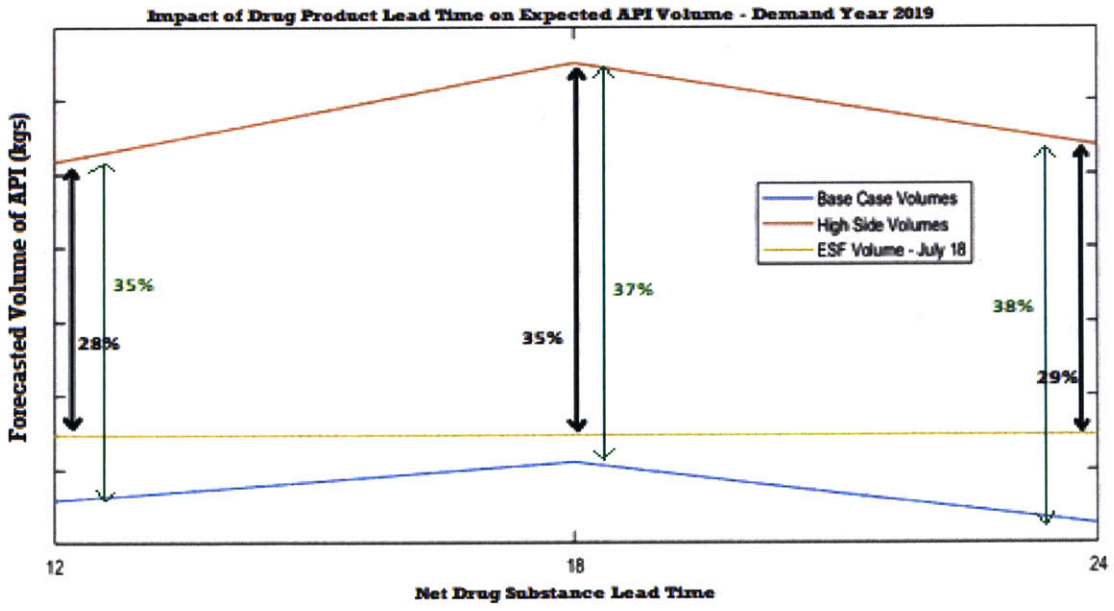


*Figure 21 - Impact of Using Different Forecasting Methods - 2*

The key takeaway from these plots is that if the net lead time for drug substance manufacturing can be reduced to 12 months, the short-term forecast can be utilized for API ordering. The expected volume ordered would be significantly reduced compared to using the long-term forecast due to the increased accuracy of the short-term forecast. Comparing the two plots, the scale of the difference between the high-side forecast from the NPI forecast compared to the short-term forecast are similar. However, when comparing the net volume difference, not percentage difference, the volume difference is lower when the drug product lead time is reduced. This follows with the forecast translation process because a smaller portion of the annual demand is shifted to the prior demand year due to the manufacturing offset, reducing the annual demand expected during growth periods.

## 6.2 Non-financial Impacts

The non-financial impacts are observed in three areas – supply chain segmentation, forecast communication and forecasting procedures. The combined effect is an organization that is required to act tactically a majority of the time to react to the impacts of changing forecasts with less time available to focus on strategic activities. Many of these impacts contribute to distrust between AstraZeneca and the supply base and are roadblocks to achieving the flexibility required to tackle the challenges of the future product pipeline. The impacts show up as inefficiencies in the supply chain and manufacturing system.

The decision to segment the supply chain into independent suppliers for subsequent nodes has a non-financial impact in addition to the financial impact shown in section 6.1. The segmentation encourages manufacturing process optimization in each of the nodes, which can result in a sub-optimal end-to-end manufacturing system. Product A is an example of local optimization for the intermediate and API manufacturing stages. As Figure 6 in section 4.1 shows, these two manufacturing stages are at different suppliers. The overall manufacturing time could be reduced if intermediate and API manufacturing were at the same supplier because the first reaction in API manufacturing matches the volume and equipment needed for the last step of

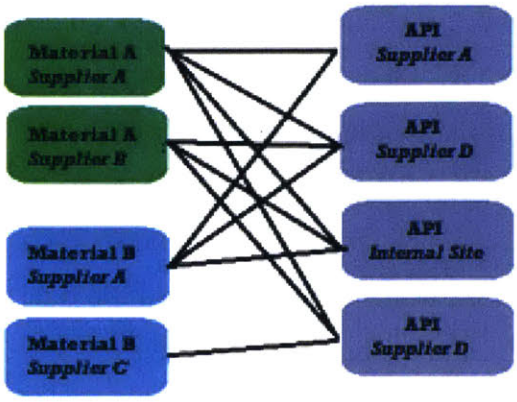


*Figure 23 - Example Manufacturing Network*

intermediate manufacturing. The first and second API reactions require different volumes and therefore different equipment to complete the two phases. The segmentation also introduces significant network management complexities, like the example network shown in Figure 23. If there were no contractual or regulatory constraints for the movement of materials, this would be a simple network optimization problem. However, the structure does not allow for this and is currently managed manually. This requires a significant amount of individual effort by AstraZeneca employees, including a dedicated, full-time employee in the case of the most complex brands.

The final impact within supply chain segmentation is the communication challenge associated with having to manage all the different suppliers and not always allowing them to communicate directly. The more suppliers involved and the more segmented the manufacturing, the greater the impact of the bullwhip effect. The segmentation causes communication delays and interface effects that result in increased inventory risk due to the bullwhip effect. The limited communication connections between nodes is a hindrance for operational data sharing and ability to manage supply chain risks at all levels in the supply chain effectively.

Limited communication into the supply base about the forecasts intensifies the bullwhip effect. The impact is evident in the increasing variation in the inventory levels as the noise in the forecast provided to suppliers increases. There are two specific aspects around communication of the forecasts, especially when there is a major change in the forecasted demand, that contribute the most to disruption in the supply chain. The effect of BCP requirements on the net forecasted demand and communication of the assumptions in the forecast are the primary sources of information distortion.

The methodology for determining the BCP required policy stock had a clear financial impact explained in section 6.1. The addition of policy stock to the forecast data introduces artificial variation in demand, resulting in the bullwhip effect. This variation cannot be directly measured in inventory performance due to confounding factors but can be qualitatively assessed. This aggregate forecast provided to suppliers does represent the estimated manufacturing needs for a given demand year but is not necessarily representative of the true demand behavior of the final product. This introduces variation in demand beyond the level in the original forecast.

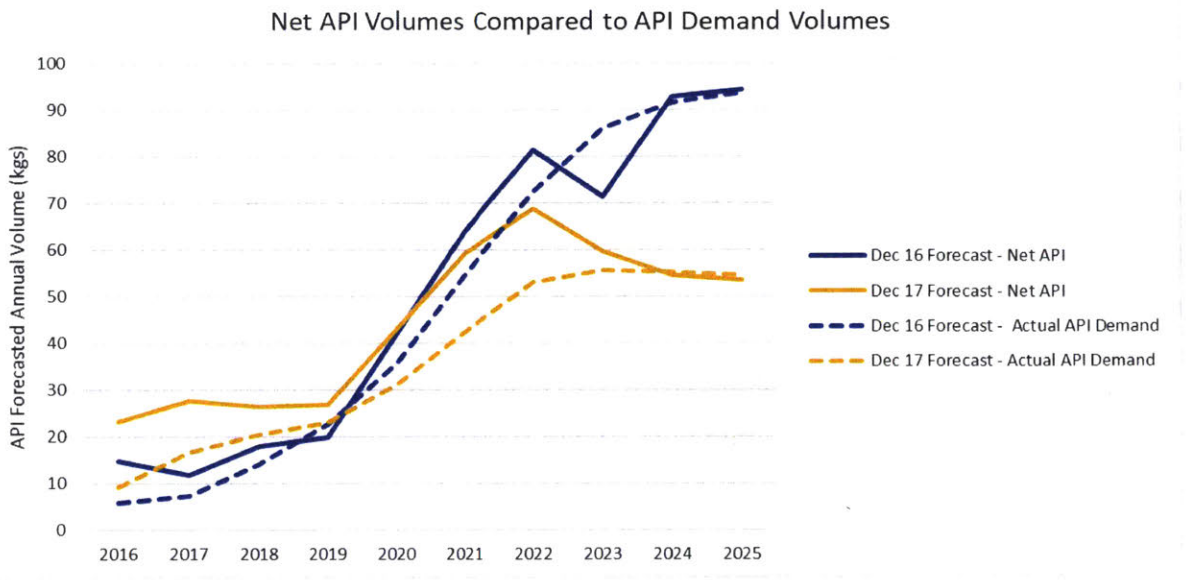


*Figure 24 - Bullwhip Effect Due to BCP Policy Stock Included in Demand*

In Figure 24, a generic demand forecast and typical BCP requirements for an NPI are used to exemplify the impact policy stock has on the overall forecast.

For the actual API demand, which does not include any inventory build-up to meet policy stock needs, the demand is smooth. Introducing the BCP, as shown by the net API forecasts, causes the demand to vary more over time, including reductions in API demand volume. The demand reduction is a behavior that is not occurring in the actual final product forecast demand. The suppliers receive the API demand forecast and can see that the demand information being shared with them does not match the publicly available information on final product demand. The obscured demand signal resulting from the policy stock builds and burn-offs being included in the demand forecast directly contributes to the bullwhip effect. Decoupling policy stock requirements from the monthly forecasted demand can mitigate the inventory risk associated with current policy stock calculation method. It will also reduce the scale of variation the supply chain sees in the forecasts. Ultimately, it can reduce the signal confusion that is currently contributing to the bullwhip effect.

Communication of the forecast assumptions is a broader issue that impacts the supply chain operation across AstraZeneca and the supply base. The current state analysis explained how the assumptions that are made to generate the high-side and base-case forecasts are not widely understood. The probability of achieving the high-side forecast is not communicated clearly and is also not consistent across brands. The limited knowledge around the forecast assumptions and

probability of success prevent risk management assessments and mitigation plans from being formed with the full knowledge of the forecast risk. Inadequate risk management can cause demand forecast disruptions to have a greater impact on manufacturing and supply chain performance. Through providing consistent and transparent information flow on the forecasts from the forecasting organization to GES and the suppliers, each of the supply nodes and GES can better manage the operational risk of forecast variation to reduce the impact of variation in demand.

All of these process and culture challenges amplify the impact to the overall supply chain system when there is significant variation in demand. Many of these items would not cause increased impacts for mature products because demand is more stable and the parties involved have more experience with the demand behavior. This allows them to informally gain some of the missing information required to adequately mitigate demand variation risks. For new products, where variation is higher, and the market intelligence is increasing, there is a greater risk of the system not being able to adequately handle the variation in demand and increase the negative response through relationship damage and poor inventory performance.

# 7 Test Case Analysis and Results

The impact assessment is an analysis of the current state forecasting, supply chain and manufacturing operations. This is critical to identify where demand variability has the largest impact on performance and processes that unintentionally magnify the demand forecast variation. The following analysis is focused on strategic changes to supply chain design utilizing the simulation tool to estimate the benefit of the changes.

## 7.1 Alternative Commercial Model

A flexible volume commitment model was tested for Product A API manufacturing. For this example, the supplier would be responsible for making 30% of the annual API demand. Since this would be a second source supplier, flexibility with volume commitments in the supply agreement is desirable as a demand variation mitigation strategy. In this model, the purchase order lead time is 15 months and manufacturing will be accomplished in single, annual campaigns. The supplier would be responsible for the upstream supply chain, including producing the intermediates for this API if desired. A flexibility parameter is defined that allows the purchase order volume to be adjusted up or down from the initial purchase order volume. At a 9 month lead time, the final volume for production is set. The supplier is required to manufacture or acquire intermediates to cover the maximum possible final production volume.

The existing data set allows for this model to be tested against the current state for two sample demand years. Two potential flexibility parameters were tested, 20% and 25%. Figure 25 shows a comparison of API orders with the new commercial model compared to the actual purchase orders placed for 2018 and 2019. Since the model does not include provisions to adjust API ordering downwards if the forecasts exceed the actual sales, it is expected that the actual PO volumes placed may not fully reflect the forecast scenario due to excess inventory. However, the comparison does allow an accurate comparison of the two models.

At first, these results are somewhat surprising. For 2018, there is minimal benefit from the flexible model compared to the actual purchase orders placed. The higher flexibility does allow for a lower volume order in 2018 since for both flexibility parameters, the model orders the minimum amount feasible based on the initial purchase order volume. Upon further inspection,

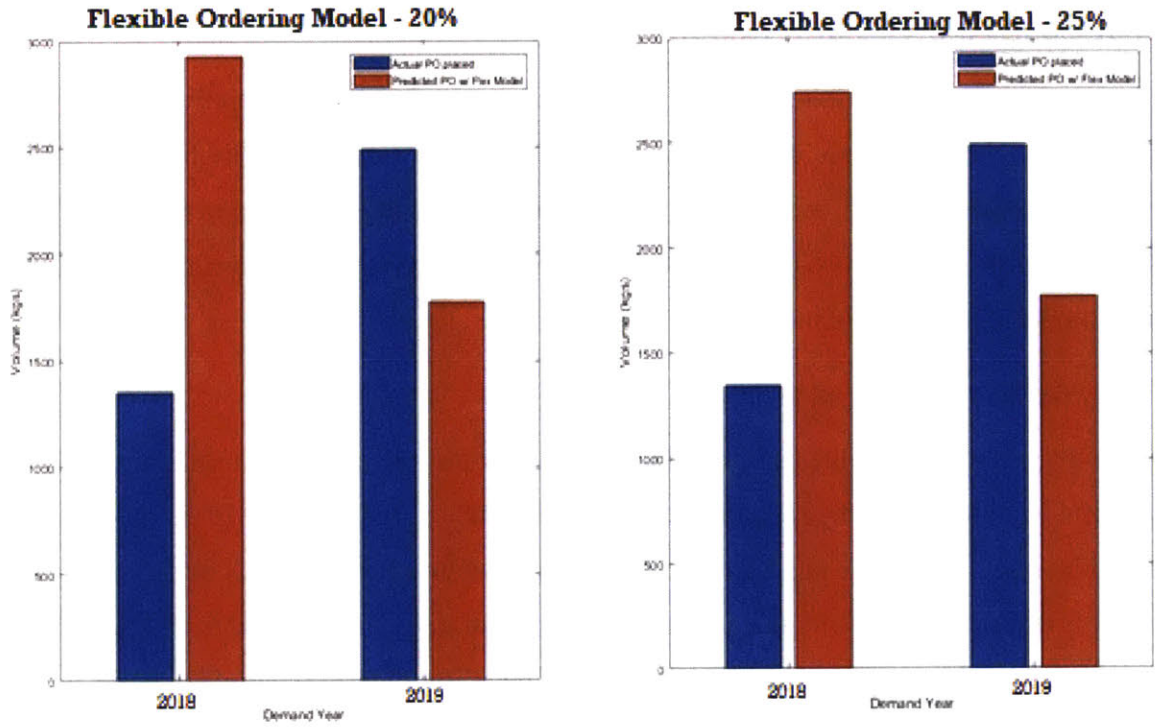


*Figure 25 - Actuals vs. Flexible Ordering Commercial Model*

this behavior was driven by the June 2016 forecast being utilized to place the initial purchase order. That forecast version had a major spike in demand volume that was adjusted downwards in subsequent forecast versions. For 2019, the benefit of the flexible model is shown through the difference in actuals to what the flexible model would have ordered. For both flexibility parameters, the final purchase order allowed the volume to be adjusted to the most recent forecast, which was lower than the actual purchase order placed. This difference is considered a cost avoidance since the inventory risk associated with ordering above the forecast is reduced.

A sensitivity analysis was also conducted on the final API volume ordered and volume of intermediates required to be held for a series of flexibility parameters. A plot of the flexibility level versus the material volume required for API and both intermediates is shown in Figure 26. For demand year 2018, the difference between the June 2016 and December 2016 forecasts is large enough that the flexible model is not beneficial until the API order volume flattens at a flexibility parameter of 70%. For demand year 2019, as you increase the flexibility from 0% to 20%, you get an improvement in ordering due to the volume adjustment at 9 months. After 20%, there is no benefit since the forecast does not change significantly. In both cases, the volume of intermediate required increases linearly with the flexibility parameters. The difference between

the API ordered and the intermediate lines is the volume of material that must be carried over into the next year for use in the subsequent campaigns. The higher the flexibility parameter, the higher the financial burden in the form of inventory the supplier is expected to take on.

The analysis highlights the ability of this model to adjust order volumes for demand variations up to a certain extend. For the 2019 demand year, this model would have resulted in ordering over 600 kgs less of API material. It has limited capability to handle large changes in forecast volumes as shown by the ordering behavior in 2018. In addition, it also requires the supplier to take on a large financial burden through the intermediate inventory which is measured in the sensitivity analysis.

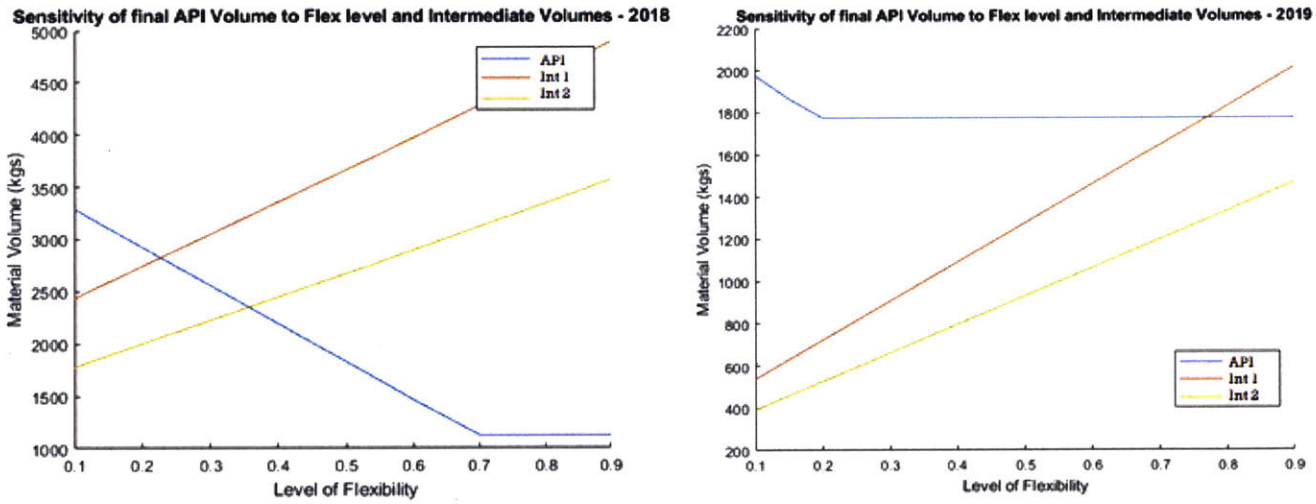


*Figure 26 - Flexibility Parameter Sensitivity Analysis*

# 8 Key Findings and Recommendations

This research provided an end-to-end analysis of AstraZeneca's supply chain and external manufacturing operations. The industry and company analysis showed that GES and the supply base have been experiencing a period of intense change since 2012 resulting from a fundamental shift in the supply chain risks profile. This shift was instigated by the increased productivity of the R&D organization and a company strategy focused on scientific leadership and returning to growth. The result was a significant increase in the number of products and new markets launched annually and more extensive lifecycle management programs. This extends the NPI phase of a product which is compounded by these products being technically complex and expensive. The operational model of GES was not developed to handle these types of challenges in an efficient and cost-effective manner. The impact of the increased variation and changing product portfolio has manifested in an inventory challenge that sparked the need for this research.

The impact of demand variability can be summarized as the bullwhip effect manifesting in the supply chains of brands, which results in poor inventory performance. The current state analysis highlighted internal policies associated with business continuity plans and supply chain segmentation that directly increased the variation in forecast demand experienced by suppliers compared to the final product demand. Limited communication around forecast assumptions and the translation process, segmentation of the supply chain and lack of standard work exacerbate the bullwhip effect increasing the impact of demand variability within AstraZeneca.

The simulation tool utilizes a two-stage supply chain model and forecast translation process to be able to assess how supply chain design and forecast variation parameters impact inventory performance at the intermediate and API stock pocket locations. This tool was successfully utilized to assess potential commercial arrangements and measure the inventory impact of certain supply chain design strategies. This is the first tool that allows GES to directly connect the long-term forecast to inventory performance, allowing for more informed supply chain design and capacity investment decision making.

GES has stabilized its internal operations to be able to manage the level of change and has standardized some of its processes. The organization is poised to make strategic adjustments to their operational model and supply chain design philosophy to support the vision of becoming a

world class pharmaceutical supply chain organization by 2025. This research highlights the two key strategic areas to focus on initially to take the first steps towards the ideal future state and re-build trust in the supply base to achieve this goal. Operational transparency and scenario based forecast planning are two concepts that, if implemented effectively, have the power to establish a transparent, connected, flexible and agile supply chain within the next five years. These changes are necessary to meet the changing needs of the product pipeline and ultimately provide lifesaving treatments to patients in a more cost-efficient and timely manner, while still providing the outstanding level of product quality and patient service experienced today.

## 8.1 Recommendations

GES leadership desired recommendations that would allow the organization to mitigate the impact of demand variability on the external supply chain and support the formation of the GES 2025 vision and strategy. A set of tactical and strategic recommendations were developed to provide recommendations that directly combat the impact of variability in the current state system, but also provide guidance for strategic development in support of the GES 2025 vision to be a world class pharmaceutical supply chain organization.

The future state goal of the supply chain is a system that is agile, flexible and synchronized to adjust to changing market demand and patient needs. The recommendations are all focused on building a foundation to achieve these future goals. Based on the analysis, operational transparency and scenario based forecast planning are the two areas to focus improvements to achieve the necessary transformation in an efficient and sustainable manner. These are the foundation for building trust within the supply base and releasing the potential for data driven continuous improvement and decision making. All these will bring GES closer to the ultimate goal of a flexible and agile supply chain built on supplier partnerships. Figure 27 shows the relationships between the target attributes of the future supply chain.

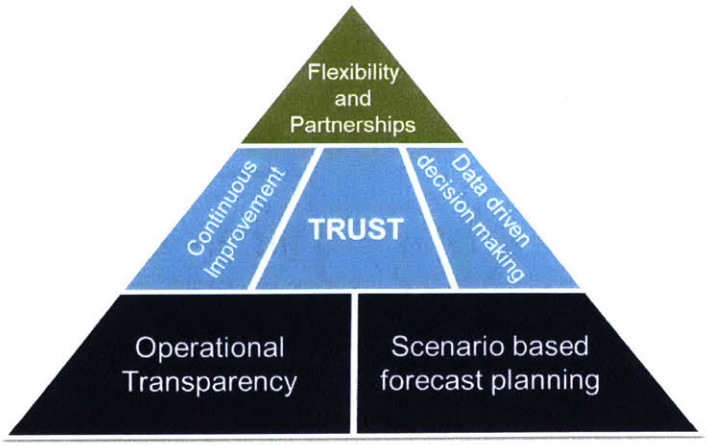


*Figure 27 - Recommendation Framework - Build the Foundation First*

## 8.2 Tactical Recommendations

Two tactical recommendations were developed that support the foundation of operational transparency and scenario based forecast planning. The implementation time frame is feasible within a year, but would require up to three years to be able to fully assess the impact of the change due to lead times and annual campaigns limiting trial opportunities. The recommendations are an alternative policy stock calculation method for BCP and implementation of a planning line for forecasts to be used for ordering instead of using the brands standard forecast scenario (high side or base case).

The impact assessment showed the BCP requirements contribute significantly to the bullwhip effect, resulting in increased demand variation and inventory risk. Decoupling the policy stock requirements from monthly demand for the first three years following a product launch can reduce the variation in demand seen by suppliers. It can also stabilize the demand signal for manufacturing planning across the entire supply chain, not just external suppliers. This not only reduces the bullwhip effect by dampening variation in the demand signal, but also mitigates some of the technical risk associated with technology transfer of new products into external suppliers for commercial launch. Policy stock is designed to protect against supply disruptions. Decoupling it from the demand variation should not impact the ability to address supply disruptions during the years just after product launch as long as it is still tied to the demand in some manner.

The proposed alternative method is based on using the expected policy stock required for the first three years post-launch to smooth demand and define a constant manufacturing volume for the first three years of production. The concept is shown in Figure 28.

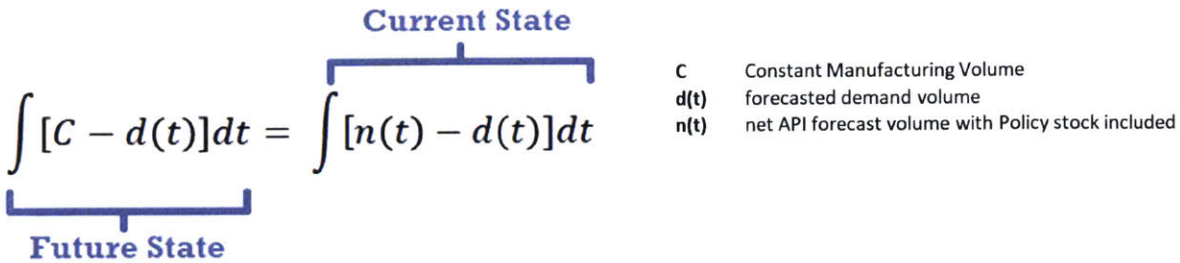


*Figure 28 - Alternative Method for Defining Policy Stock Requirements for NPIs*

The future state and current state models require the same volume of policy stock to be manufactured over the three year period. A consistent net manufacturing volume was selected as the target demand model for NPI years 1 – 3 to provide stability for the supply base. Figure 29 compares the current state manufacturing volumes compared to the proposed state using generic NPI forecast data for years 1 – 3. The proposed model trades flexibility in policy stock volume with stability in forecast demand. Initially, this model requires the policy stock volume for year 1 to be higher than the BCP design volume to allow for less stock to be built in year 3 even as demand is increasing. The additional volume can be used as risk mitigation against any spikes in demand early in the lifecycle.

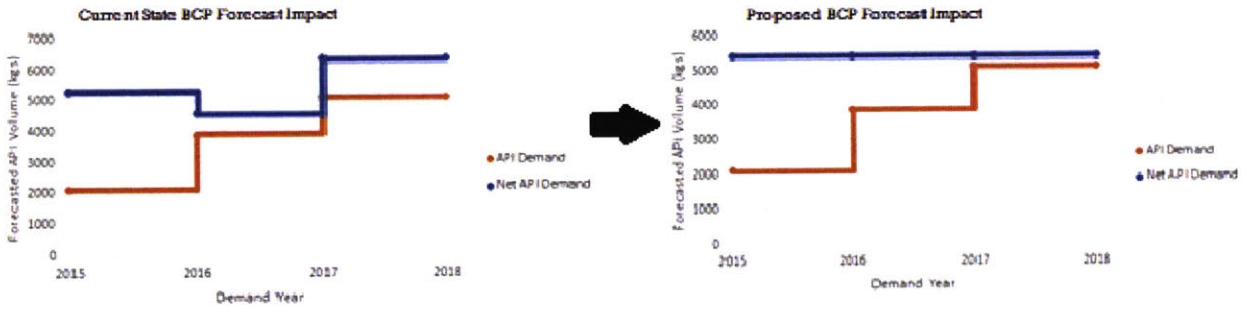


*Figure 29 - Proposed BCP Manufacturing Volumes*

A feedback mechanism can be introduced through a review cycle where the manufacturing level "C" can be reviewed after each new forecast release. The review process would serve a dual purpose. It allows the brand team to review any significant changes in demand that would require the manufacturing volume, C, to be shifted up or down. A secondary benefit is that the proposed method would add a more formalized brand review of the forecast impact on external manufacturing, increasing visibility and understanding.

The second recommendation is to develop a technically defined planning line to base purchase orders on instead of the boundary scenarios defined by the NPI forecast. The boundary scenarios are the base case and high side forecasts. For NPIs, most brands determine purchase order volumes on either of the boundary scenarios based on the therapy area and brand strategy. Figure 30 shows how the planning line would compare to the forecast scenario that would currently be used. The planning line is a reduction from the high side NPI forecast that is "technically defined".

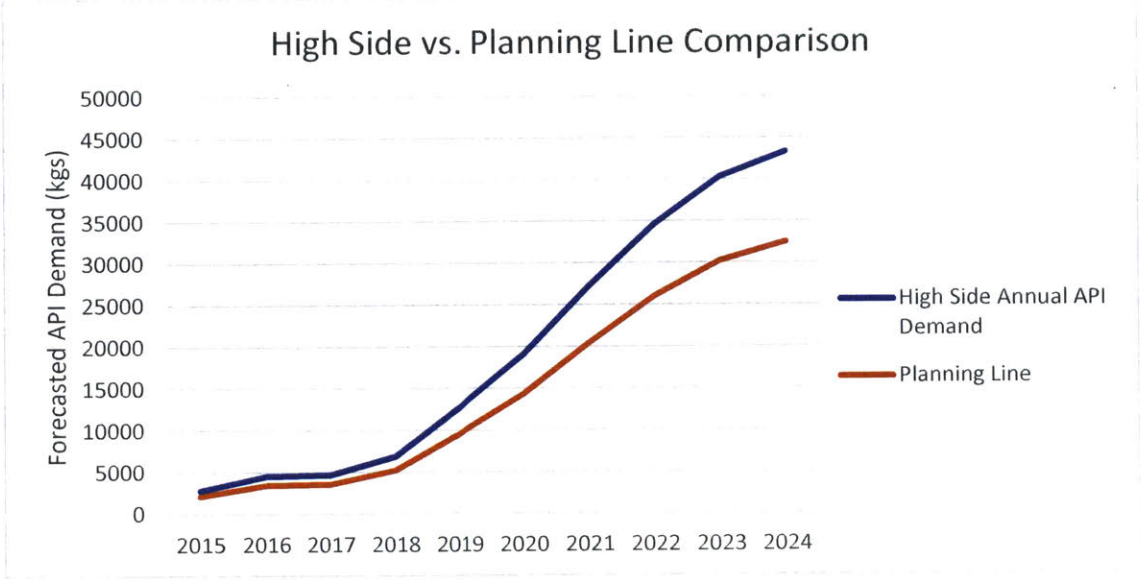


*Figure 30 - Proposed planning gap compared to current state*

Defining the gap between the high side forecast and planning line is the power behind this strategy. The percentage difference between high side and planning line is "technically defined" because it is based on a detailed understanding of the manufacturing process and product risks rather than a selecting a percentage or using only market data to define the gap. Using operational data such as number of batches, cleaning intervals and shift schedules, flexibility for a product is defined through knowing what actions are required to increase the production volume. For example, if the planning line is 15% below the high side forecast, the team would understand how many batches of material, how much time and what raw material inventory are required to increase production to the high side forecast. This manufacturing information scopes the operational risk and defines a series of actions required to increase production volumes if necessary. Product risks and market intelligence are utilized to define the probability of the high side forecast and planning line of occurring to understand the brand risk associated with not planning to the high side.

The concept of planning to a lower volume but protecting the high side is used in several other industries. It is not as common in pharmaceuticals because it has the potential to impact patients negatively if the high side forecast comes to fruition if the manufacturing system is not capable of to adjusting to produce the additional volume. Using technical product data and manufacturing process information to define the gap between the high side forecast and planning line reduces that risk by defining a series of action required to ensure that the production increase

is feasible. The planning line mitigates the risk of sales not achieving the long-term forecast level while maintaining the capability to achieve the high side volume. This introduces flexibility into the manufacturing system on the basis of technical definition instead of market intelligence and brand trends, which are harder to define and successfully mitigate risks.

## 8.3 Strategic Recommendations

The two strategic recommendation areas have already been defined as operational transparency and scenario based forecast planning. These recommendations will help GES adopt a science-led approach to supply chain management that aligns directly with the corporate strategy of science-led R&D and product development. While closely related, each recommendation represents a slightly different approach towards building the flexibility and agility required to meet the transforming needs of AstraZeneca's product pipeline and the changing pharmaceutical industry. They are critical to building the digital infrastructure required to achieve streamlined communication throughout the supply chain and synchronization.

### 8.3.1 Operational Transparency

Operational transparency is the sharing of information related to manufacturing processes, performance and risks between supply nodes. This is inclusive of links between AstraZeneca and its suppliers and between suppliers in adjacent manufacturing nodes. Operational transparency is not open book costing or the unfiltered sharing of information across brands and all supply nodes. It is selecting the right information for the right purposes to be shared in an open manner to improve process knowledge, risk management procedures and system performance. It is key to enabling data driven continuous improvement, cost intelligence for financial improvements, data transparency and identification of disruption behaviors for supplier relationships and has the power to unlock technically savvy commercial arrangements.

There is an infrastructure and capability building component to this recommendation. Operational transparency relies on being able to learn, monitor and understand the manufacturing process at each node in the supply chain. In the world of global supply chains and the volume of outsourced manufacturing at AstraZeneca, this equates to the development of electronic process monitoring and data collection in near real-time. The data can be used to monitor process performance, reduce communication time, enable proactive intervention measures and improve manufacturing planning and capacity analysis.

Parallel to the digital infrastructure are the capability building activities within AstraZeneca and key suppliers to be able to adequately use, understand and benefit from the increased manufacturing transparency and data availability. This requires closer collaboration between GES and the PT&D organizations and emphasis on manufacturing knowledge as a skill necessary in GES, but one that can be learnt after joining the organization. This is a shift in the desired skill sets and capabilities in the employee base. However, it is one that can be built through spending more time at the supplier manufacturing sites and having data available to better understand processes without having to be on-site full-time.

This recommendation is supported by the findings in the literature review around the power of information sharing as a mitigation strategy for the bullwhip effect. The external benchmarking also highlighted the importance of a "boots on the ground" approach to interacting with suppliers and the importance of understanding suppliers' manufacturing operations if the interaction is going to be anything more than transactional. This is also a necessity for technically complex products, parts or manufacturing processes. AstraZeneca's product pipeline is trending towards more complex API manufacturing processes and in some cases specialized manufacturing technology. Operational transparency will be key to successfully developing a supply chain and supplier relationships for these products in the future.

Based on the manufacturing tours and discussions with various supplier and AstraZeneca employees, there is untapped potential in manufacturing process improvements that may not be directly related to the actual chemical reactions. An initial focus area for operational transparency in the manufacturing process is a detailed capacity analysis to truly understand where time is spent in the manufacturing process, measure asset utilization and identify opportunities to reduce process time waste and release currently reserved capacity. This concept will be further explored in the proposed pilot program.

### 8.3.2 Scenario Based Forecast Planning

A scenario is a set of assumptions that define what the demand forecast represents. In the current state, the two known scenarios are high side and base case. While these are both valid scenarios, the assumptions that generate these scenarios are not consistent across brands or understood consistently throughout the organizations that use the forecast. The concept of scenario based forecast planning is to tie a story that describes the assumptions and risks to be

communicated with the forecast volumes. The forecast must be the story plus the number to improve consistency of communication and allow for better understanding of risks.

The scenario should be developed concurrently with the forecast to be able to adequately capture major assumptions and risks. A probability of success should be tied to the scenario based on how it is built up. This probability may not always be able to be scientifically defined and will require assumption but will increase clarity around the likelihood of the forecast actually being achieved. The teams should be able to answer questions like - is the base case volume near 100% probability of occurring? How has high side forecast been adjusted for risk? This provides insight into the confidence associated with the volumes and allows teams within AstraZeneca to refine inventory policies to match risk. For the suppliers, this information will provide insights that are not widely available today and is powerful data to improve their risk management practices for individual brands. Robust risk mitigation plans

The long-term strategic benefit is building trust with the supply base and increasing the confidence in the forecast data provided to the suppliers. The increased transparency around forecasts and assumptions does reveal more information about AstraZeneca's operations and strategy, but the benefit of improved risk management capability and consistent understanding of what the forecast represents, and the associated risk better prepares the supply chain to mitigate the inevitable demand variability that will be experienced for NPI. This is a critical step towards building partnerships with strategic suppliers and is more broadly applicable beyond NPI and drug substance manufacturing. Internally, GES will be better informed when making capacity investment decisions because the assumptions and risks are more widely and consistently understood. The scenario information will also be helpful in defining a planning line and the risks associated with planning to a volume that is below the forecasted level. These practices at a large scale will unlock the potential to implement the "plan to protect" approach across the portfolio, greatly reducing the inventory risk associated with under-performing to the long-term forecast. The cost avoidance potential is on the order of tens of millions of dollars in inventory reduction.

The primary purpose of this recommendation is to increase information sharing to reduce the impact of the bullwhip effect. Information sharing and transparency are one of the most common ways to combat the bullwhip effect. This type of transparency is a positive reinforcing cycle

where the more information shared by AstraZeneca, the more willing the suppliers will be to share information with AstraZeneca, which increase trust. As trust increases, both parties should be willing to share more information. The cycle is what will drive AstraZeneca and the suppliers from a transactional relationship to a partnership. Supply partnerships are based on trust and mutual benefit. The information shared is a powerful improvement tool for both organizations and strategically positions them to meet future needs of each other.

# 9 Conclusion

This thesis investigated the financial and non-financial impacts of demand variability on external manufacturing operations and developed a measurement methodology for estimating the impact of variation on inventory performance. This analysis and subsequent measurement methodology resulted in the development of a set of tactical and strategic recommendations to help the GES organization within AstraZeneca mitigate the risk of demand variability and modify processes that contribute to variation in the demand forecast. The approach started with a current state analysis of the supply chain and manufacturing operations for two products. This included site visits and interviews with suppliers to ensure the voice of the supplier was represented in the research.

The current state analysis also extended to an industry and company level analysis to identify trends that are contributing demand variation and exacerbating its impact on the supply chain. Using the data collected in the current state analysis, a simulation tool was developed to measure the impact of demand variability on inventory in a two-stage supply chain. The tool was designed to be a decision assist tool. Finally, the results of the impact assessment, simulation tool and literature review were used to define and assess recommendations. The results indicate the bullwhip effect is the source of the major financial and non-financial impacts. Two tactical recommendations and two strategic recommendations were developed. Pilot program implementation guides were developed to support implementation of the two strategic recommendations and follow-on work and are shared in Appendix A.

This body of work was able to successfully achieve the two research objectives set during the initial problem formation of developing a method to assess and quantify the financial and non-financial impacts of demand variability and identify process improvements and strategies to mitigate the risk of demand variability. There is an opportunity to further this research through continued development of the simulation model and the implementation of the two pilot programs. The model can be developed to be more forward thinking through introducing probabilistic variables and potentially a Monte Carlo simulation for forecast variables. The model could also be transitioned to be more product specific to allow for more accurate analysis rather than just as a decision support tool.

The two pilot programs in Appendix A are targeted implementation plans for the strategic recommendations and complement the tactical recommendations that address the policies and procedures within AstraZeneca that amplify the impact of demand variability. Change management and working closely with the strategic suppliers will be critical moving forward to stimulate sustainable change within AstraZeneca. Much of this work ultimately needs to result in an industry level change to be sustainable. Education and information sharing on new commercial models and technology implementation can help move the major pharmaceutical and CMO industries towards supply relationships that are flexible, agile and beneficial for all parties involved. This research is an initial step toward the GES vision of becoming a world class pharmaceutical supply chain organization and continued work in digital infrastructure and supplier relationships is necessary to refine the strategic and tactics to achieve that vision.

# Appendix A – Pilot Programs

The strategic recommendations are high level concepts that represent a way of doing business. Two pilot programs were developed to take the first steps towards achieving operational transparency and scenario based forecast planning. These ways of working are step function changes when compared to the current state and the pilot programs provide an incremental step that is measurable and will help build the framework and foundation for further expansions. They also act as a proof of concept with benefits that can be measured through inventory performance or supplier and employee surveys.

## i. Pilot 1: Forecast Communication and GES2025

The goal of this pilot program is to design an alternative commercial arrangement that meets a defined band of flexibility based on the specific product. This pilot addresses the forecast-based scenario planning recommendation with complementary initiatives and strategies being considered in GSC&S included as applicable. It requires cross-functional collaboration between GES, GPPS, GSC, Procurement and Operations in addition to collaboration with the API supplier and potentially a RSM supplier. While it should be sponsored by the OSLT (Operations Senior Leadership Team), the team should be at the working level with the OSLT in an advisory role only. The pilot would require both financial and resource investment.

Due to the conditions of the new supply agreement contract, a flexible manufacturing volume solution is required to cover Product A API demand at the second source. This provides GES and AstraZeneca with a unique opportunity to develop a pilot that reflects the step change in supply chain strategy, visualization and ways of working that is required to achieve the future vision of supply chain and manufacturing operations at AstraZeneca. The pilot is a way to develop a body of knowledge about the implementation of different strategies and technologies as well as providing evidence to support broader change in the future.

For API manufacturing at the second source, a traditional flexibility model is being proposed that establishes a fixed volume commitment with the purchase order and then allows the final production volume to be a range above that based on the predefined level of flexibility. This is a well-tested model within AstraZeneca that is currently being used on another brand. Simple forecast to purchase order modelling showed that there is a benefit to using this model.

However, it may not be able to fully cover the volume flexibility required for a second API source on this product.

This pilot outlines a phased approach for implementation. It is meant to be a guide, not a recipe for developing a flexible, agile and informed supply chain and manufacturing operation. While Product A is an ideal candidate for the pilot due to campaign timing and a high level of forecast variation, the AstraZeneca team culture, supplier willingness, future strategies and statements of work at the supplier should be considered when finalizing the product selection for the pilot program. The framework is adaptable to other products if they are better candidates. This pilot is directly aligned with the future requirements of the AstraZeneca product pipeline that have been shared internally and with the strategic suppliers as well as a vision for the future of supply chain, operations and supplier relationships. The cross-functional team will help drive alignment to a single vision.

A three-phase approach with significant pre-work has been developed to allow for the work to be completed in management chucks. The resource structure of the pilot is shown in Figure 31 and descriptions of each phase and the expected deliverables are outlined below.

**Core Team Organizations:**
- GES: asset planner and supply chain lead
- PT&D: Technical focal
- GSC: GSP, supply chain visualization team member, forecasting (optional)
- Procurement: contracts
- Operations: formulation and packaging planner or similar strategic role as asset planner
- Equivalent supplier roles

*Support Team Organizations:*
GPPS, Commercial, IT, Quality

**Duration:**
*Development:* Pre-work, Phase I and Phase II – 6 months
*Implementation:* 2 years (two annual campaigns of API)

**Brand/Supplier**
- Must be a brand that will remain in the NPI phase for the duration of the pilot
- The supplier should be a strategic supplier and ideally have strategic suppliers as upstream nodes in the supply chain

*Figure 31 - Supplier/GES 2025 Pilot Program Structure*

### i. Pre-work

The pre-work is scoped to provide the background necessary to build an initial business case for pursuing the pilot program and gain sponsorship from the OSLT. The pre-work can be led by GES, but the other functions should be consulted to make sure adequate amount of information is collected and gain initial stakeholder buy-in from the organizations. The following

types of information should be collected. The list is not exhaustive, but should provide the correct reference for what type of information will be required.

- Generate a high-level demand envelop to estimate the extent of flexibility that could be required for the particular brand/supplier based on the existing base case and high side forecasts
- Estimate the potential inventory savings of this alternative supply arrangement compared to the current state using historical forecast data and the simulation tool
- Build a simplified block diagram that is representative of the manufacturing process and identify what a 'synchronized' manufacturing process would look like
- Identify potential candidates for AZ team/Supplier/Brand combination for the pilot program based on team cultures and the future demand picture for the brand
- Present findings to GES leadership team to get support and then develop the OSLT pitch

The deliverables for this phase should include a pilot charter document, candidate brand and supplier and a principles of working together document. The charter is an outline of the problem statement, scope, data required, resources required and expected deliverables from the pilot program. It should also identify a sponsor who will champion the pilot and be the approver of the charter document. The sponsor should be the pilot program's champion and is responsible for ensuring the team gets the required resources and support. The principles of working together document is complementary to the charter and outlines the behaviors and expectations of all parties involved in the pilot. This should align with the future vision for operations and supplier relationships at AstraZeneca.

### ii. Phase 1 – Forecast Scenario Development

Phase 1 is a joint effort between GPPS, Commercial, GES Asset Planners and Procurement to analytically define the envelop of forecast scenarios the candidate could experience. This requires probability of occurrence for each scenario outlined. The analysis should include the volumetric extremes, likely scenario and an extremely likely scenario. Data is required from all these organizations and includes forecasting data and insights, current and future supply agreements, supply chain design and current inventory model and stock levels.

The deliverables from this phase are all focused on creating a robust forecast scenario to use in the pilot while also documenting the process for future use and improvement. The analysis should provide an analytically defined and probabilistic outline of potential demand scenarios that the candidate supplier could experience, a detailed list of forecast assumptions and scenario description. These deliverables will support a risk analysis that can be used to generate a timeline of key milestones that will have a major impact on expected demand volumes (new market launches, on-going clinical trials, patent cliff, generic competition). This information is critical for defining the risk profile and triggers for demand variability.

### iii. Phase 2 - Supply Chain Engagement and Pilot Definition

With the analysis to support the negotiation of a development arrangement completed in phase one, work can begin with the candidate supplier to establish the contractual basis for a joint pilot program with AstraZeneca. The charter document should be the primary reference for the contract and relationship with the supplier. This phase is the longest and represents the majority of the scope of work within the pilot. It has been separated into three mini-phases based on the type of work.

*Phase 2.1 – Supplier Buy-in:* Supplier buy-in and assignment of a pilot sponsor who will also sign the charter document. Any adjustments based on supplier feedback can be added at this time, but any changes must be bought in by all stakeholders and should not under any circumstances step backwards from the future vision and ways of working. The stakeholders from both companies should work together to develop a launch workshop agenda based on the charter. The goal of the workshop is detailed definition of the pilot program and an implementation plan. Upon completion of this phase, the charter document should be signed by all stakeholders, teams assigned to support and resources allocated for the work.

*Phase 2.2 – Launch Workshop:* The first step for the workshop is to define the pre-work required for the workshop based on the agenda. This includes clearly defining what data is required, topic area presentations, ground rules, who needs to be involved full-time in the workshop and who is required for on-call support. All attendees should attend in person and the workshop should be scheduled and resourced for a full week. Based on the core team, a total of 15 – 20 individuals should be expected to support the workshop. It should be facilitated by someone outside of the core team who is trained as a facilitator. An example workshop outline is provided below:

- *Day 1:* Introductions, ground rules review and agreement, charter document review, Supply Chain review, forecast scenarios review, risk identification brainstorming/working sessions
- *Day 2:* Review of Day 1, risk mapping, initial brainstorming sessions for how to address the outlined problem, idea development sessions, first idea down select
- *Day 3:* Review Day 2, working session of idea from first down select, team presentation on ideas, risk review, final down select
- *Day 4:* Review Day 3, road map development, phase planning working session and report out, action plan (action plan will likely be added to throughout the week), presentation development
- *Day 5* (half day): review of the week, presentation dry-run stakeholder report-out. Both sponsors attend as well as other major stakeholders from AstraZeneca and the supplier

The deliverables from the workshop include the pre-work analysis, workshop notes and photo documentation, implementation plan/road map, action list and final presentation.

*Phase 2.3 – Pilot Development:* This is the final phase in development and results in a detailed implementation plan. The statement of work includes developing the detailed plans, supporting data, analysis and infrastructure required to execute the pilot. During this phase, risk management and identification of any new risks or opportunities are recorded. The scope of the pilot should not be expanded beyond what was defined in the workshop. The exact campaigns to implement on, measurement methodologies, KPIs and a detailed project plan. A significant amount of focus should be placed on real-time process measurement (not e-batch records) and how/what should be measured as indicators of performance. A technology strategy and plan should be clearly defined as well as how the investments will be made to fund the pilot. The deliverables from this sub-phase are the documentation required as part of the implementation plan.

### *iv.* Phase 3 – Implementation

This is the execution of the detailed implementation plan. Suppliers will 'own' certain parts of the pilot. A cross-functional AstraZeneca team should be on-site for a large portion of the campaign to assist with monitoring as well as continuing to identify and assess new risks and opportunities. As part of the implementation plan, the focals identified for functional

representation or pilot activities should be the primary contacts for communication of changes, issues and progress to ensure timely and consistent communication. This phase requires the highest level of investment because it is investment in products, technology implementation, resources and inventory. Patience and flexibility will be critical to the success of the pilot.

The deliverables from the implementation phase will be defined during Phase 2, but should include performance metrics, data analysis, shared learnings and information sessions on the pilot to the broader communities within AstraZeneca and the supplier. The implementation phase is the evidence to inform decision making for strategic changes to meet the future challenges in the product pipeline. It should be used as a body of evidence and platform to implement change across Operations and Supply Chain.

### v. Target Outcome

This pilot program addresses many of the impacts identified throughout the course of the research and builds the foundation based on scenario based forecast planning. The integration with other stakeholders is key to building support for the GES focused improvements and also enriches the potential impact of the pilot. Success of the pilot is defined by generating enough empirical data to support strategy development, decision making and investment for the GES 2025 vision and potentially support the development of the Operations 2025 vision.

## II. Pilot 2: Process Control and Capacity Analysis

This pilot is focused on improving process knowledge and capacity analysis in support of improving operational transparency. The pilot is based on applying manufacturing process control, a widely used statistical analysis methodology focused on variation reduction, as a tool to reduce process time variation. The method is based on using statistical analysis and process definition models for the manufacturing process of interest to identify parameters that contribute to variation in the output parameter(s) of interest. Process capability analysis uses statistical analysis to determine if a process is capable of meeting the specification requirements for the desired output. This is an opportunity to drive science-led behavior in supply chain operations.

The process control methods can be applied to the batch manufacturing process to better understand the source of variation in stage processing times and identify opportunities to reduce variation without impacting product quality. The Continuous Process Verification (CPV)

program at AstraZeneca is based on Statistical Process Control (SPC) and capability methodologies as a scientific basis for showing quality via process monitoring instead of test. This pilot program recommends using the same analysis implementation framework and applying it to stage process times in the chemical manufacturing process instead of quality.

### i. Process Control Overview and Application

Process control is a methodology that utilizes data monitoring of a manufacturing process to assess the level of variability, identify inputs that contribute to variability and understand what inputs are most significant. Statistical Process Control is a methodology within process control that is a process diagnostic tool used to identify if there are non-random process disturbances occurring [8]. The analysis generates control limits specific to the manufacturing process. The purpose of process control is to first and foremost to maximize the quality performance of the final product. Secondary goals include increasing throughput, improving flexibility and reducing costs. This is pilot program is focused on the secondary goals with the understanding that the primary goal of quality is already met. A ground rule of this analysis must be that any changes to the manufacturing process must not impact the final quality of the part.

The process control hierarchy has three phases that are differentiated by the maturity of the process control. Descriptions of each phase are provided below. [8]

*Stage 1 – Reduce Disturbances:* The analysis is focused on identifying sources of non-random disturbances and eliminating or reduces those sources Implementation of standard operation procedures is a critical step before any data collection or analysis can begin.

*Stage 2 – Reduce Sensitivity:* Through design of experiments, variable sensitivities are defined, and the process is optimized to minimize the output variability.

*Stage 3 – Measure outputs and manipulate inputs*: Feedback control of outputs is the final step that enables the active monitoring and control of inputs to manipulate the outputs to maintain within the control limits.

For improving process knowledge and capacity planning, the focus is only on Stage 1 Process Control - reducing disturbances. The goal is the measure the inputs and stage processing times to understand if there are any identifiable sources of disturbances and if those disturbances can be minimized. Stage 2 would be a future opportunity. However, Stage 3 is out of scope

because actively controlling the inputs would directly impact product quality and stability of process time is a secondary objective, with product quality being the critical output. The SPC analysis will likely be a multivariate analysis, but the single variable analysis should be completed initial to determine if multivariate analysis should be used instead.

The benefits of implementing SPC are twofold – real time process monitoring, and advanced capacity analyses are key enablers for a supply chain of the future.

> *Real Time Process Monitoring* refers to the data infrastructure that accurately tracks critical process parameters, performance and progress electronically and at near real-time speeds. This capability is critical for proactively identifying potential delays or issues within the manufacturing procedure, but also aids with informing the larger supply chain on status and issues. For process time monitoring, it can enable the ability to predict if a certain process stage will take longer than planned and allow the manufacturing planning to be adjusted as needed if there would be an expected downstream impact.
>
> *Advanced Capacity Analysis* is the primary objective of applying SPC with process time as the output of interest. The data generated from the process monitoring system is a powerful educational and continuous improvement tool. The process data provides a wealth of information around performance and plant operations. Bottleneck identification, true equipment utilization rates, changeover times and variation in process time all create a digital footprint of the manufacturing system that is data based. Actual utilization rates represent a more accurate measure of how a facility is performing and where there are improvement opportunities compared to the planning utilization rate[5]. This information combined with lean and continuous improvement methods has the potential to relieve capacity constraints through scientifically defined planning bars and the ability to make data driven risk decisions about planning schedules.

The pilot program is focused on leveraging the existing SPC infrastructure in AstraZeneca in the form of the CPV program and extend it to process stability control. The goal of the pilot is to test the ability of SPC to reduce variation in manufacturing process times and allow for

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[5] Planning utilization rate is a utilization rate calculated for equipment based on allocated machine time in the manufacturing planning system.

improved asset utilization to free up currently reserved capacity. The pilot also builds the foundation for a digital infrastructure for future use. It directly supports the recommendation of improving operational transparency and will be an initial step into data driven continuous improvement.

### ii. Suggested Pilot Program Overview

The scope of this pilot program is smaller compared to the *Forecast Communication and GES 2025* pilot and its implementation is more targeted. The three phases break the work down based on function and act as a gated process for the analysis to progress.

*Phase 1 - Data availability:* The CPV program has already been rolled out to several different manufacturing units, but the extend of implementation into the supply chain is unknown at this point in time within GES. The purpose of the first phase is to review the Continuous Process Verification (CPV) framework, implementation plan and current state of roll out. Identify if CPV had been implemented or plans to be implanted in Q1 or Q2 of 2019 in any API manufacturing facilities. If CPV has already been implemented, data sets should be available for use in an initial process time analysis. If implementation is planned for a future date, work with the team to help define the data collection infrastructure and insert a team member into the implementation to monitor progress and access the data. If implementation is not planned, you need to follow the full CPV implementation process modified for a focus on process times

*Phase 2 – CPV Integration and Analysis:* Using the CPV framework, develop the technical process knowledge and strategy. Review the product portfolio and manufacturing schedule to see when commercial API campaigns are being done at the Macclesfield Pilot Plan or SweOps API manufacturing to generate a test case. Utilizing product information within PT&D, define the manufacturing process model for a single stage to be modelled initially. This could be extended to match what the typically CPV implementation looks like. Finally, select a target API campaign for implementation based on project lead times and any IT infrastructure additions for real time process monitoring.

Once the data has been collected, follow the process control methodology laid out in the CPV program to identify sources of variation such as process stage inputs like weight, humidity and volume. Working with PT&D, a technical process and data review can be used to help define which parameters can be controlled or modified to reduce the variation in process time. Using

this information, define control limits for process time and track performance to these limits on subsequent runs for verification. Monitoring of input of parameters of interest should be done as well.

*Phase 3 – Capacity Analysis:* The intent of the control limit analysis is to provide scientific evidence of manufacturing process times to compare against the planning bars used in scheduling. An analysis of the current planning bars compared to control limits will flag any bar that is outside of the range and recommend adjustments as needed. In addition to the planning bars analysis, a design of experiment should be completed based on the technical review results to test the impact of certain variables changes on the outputs. It is critical to ensure that any changes do not impact the quality of the product. Using AstraZeneca and the suppliers existing continuous improvement framework, identification of any process improvements should be recorded for future test and exploration.

### iii. Outcome

Completion of this pilot program has both infrastructure, capability and improvement opportunities. Successful completion requires the development of a digital infrastructure for near real-time process monitoring and data collection. This is a base line requirement for AstraZeneca if they want to improve supply chain visualization and enable synchronization of manufacturing stages. It works to develop SPC capabilities within the team and provides experience with analysis of manufacturing process data that previously was harder to achieve. The increased capability of AstraZeneca and supplier employees acts as a multiplier of value for the patients when you consider the continuous improvement and risk management benefits that result from the increased data availability and accuracy.

The improvement opportunities provide the most short-term benefit. This modified SPC strategy based on process times can be utilized to improve manufacturing planning procedures and allow planners to better understand capacity risks associated with reduced buffer times. This is an opportunity to take a science led approach to manufacturing planning as well as proactively and improve asset utilization, potentially reduce buffering and release currently 'reserved' capacity. This can be accomplished through analytically defining the process times for the given product and stage and defining control limits to be used for allocating production time on a specific asset. The result is a manufacturing process that has a statistically defined manufacturing

bar for each stage in the manufacturing process. The bar represents the amount of time and asset capacity that must be allocated per batch. Proactive monitoring can alert the supplier and AstraZeneca if additional manufacturing time may be needed and adjust plans accordingly. The manufacturing buffers can also be scientifically defined, potentially leading to releasing currently reserved capacity and improving asset utilization. Finally, the knowledge bank of process data is a powerful continuous improvement and manufacturing education tool. The benefits of this are hard to measure, but both support the data driven continuous improvement and decision making to allow for a flexible and agile supply chain in the future.

# Appendix B – MatLab Scripts

This appendix contains the relevant MATLAB scripts that were used to execute the simulation described in Section 5.2. It contains the following scripts and functions:

- purchase_order.m
- leadtime_flex.m
- flex_volume.m

---

```
%Script:   purchase_order.m
%Inputs:   none
%Purpose:  Base simulation file where functions are executed

%this script is used to convert forecast and supply chain design data into
%a purchase order schedule to be used in a simulation.

%read in the forecast data for the available timelines and the supply chain
%design parameters from the input file
file = 'sim_input_file.xlsx';


%[PO_schedule_int, PO_schedule_API, cum_int, cum_api] = leadtime_flex(file);

%Flexible volume
%you need to Uncomment this section of the code if you want to run the
%flexible volume data.
%the flex_volume() function generates PO orders for each phase of ordering
%and then reports on the sequence and time of the orders as well as the
%cummulative volumes ordered for a given demand year.
[PO_schedule_int, PO_schedule_API, cum_int, cum_api] = flex_volume(file);

xlswrite('sim_input_file.xlsx',PO_schedule_int,5)
xlswrite('sim_input_file.xlsx',PO_schedule_API,6)
xlswrite('sim_input_file.xlsx',cum_api,7)
```

---

```
%Function: leadtime_flex.m
%Input:    simulation input file
%Purpose:  generate a purchase order schedule and volume commitment
%          tracking timeline

%this function takes the forecast data and parameters files and returns
%a table with times and purchase order volumes for intermediates to be
%used as the input file for the simulation. The variables in play are
```

```
%the lead times and number of annual campagins.


%UNITS
%   time [days]
%   volumes [kg]

function [PO_dataI, PO_dataA, cum_int, cum_api] = leadtime_flex(file)
%bring in data from the excel file
forecast_data = table2array(readtable(file,'Sheet','Forecast_Data'));
parameters = readtable(file,'Sheet','Parameters_LT');

%bring variables out of the parameters file
%define the design parameters to be used in the analysis
LT_int = table2array(parameters(1,2)); %lead time in days required for intermediate
LT_api = table2array(parameters(2,2)); %lead time in days required for API
manf_rsm = table2array(parameters(3,2)); %avg. manf time for longest lead time RSM
manf_int = table2array(parameters(4,2)); %avg. manf time for annual intermediate manf.
manf_api = table2array(parameters(5,2)); %avg. manf time for annual API campagin
api_camp = table2array(parameters(6,2)); %number of API campagins completed in a year


%check that this model is valid to use (i.e the RSM lead time is within the
%intermediate planning horizon (Intermediate LT - intermediate manf. time)
if (LT_int - manf_int - manf_rsm) < 0
   fprintf('this model cannot be used because the RSM leadtime exceeds the intermediate
planning lead time\n')
   return
end

if (LT_api - manf_api) < 0
   fprintf('this model cannot be used because the API leadtime is shorter than the required manf.
time\n')
   return
end
%initialize the initial simulation time to zero
time = 0;
max_time = 1000; %the simulation will only ever run for 5 years
years = [0 0 365 730 1095 1460 1825 2190 2555 2920 3285]; %represents 2016 to 2025
%check if the supply chain design has more than one campagin per year. If
%there are multiple campagins, then it uses the imported forecast data to
%generate a new forecast_data array that is adjusted for the campagin
%timing.

if api_camp > 1
   forecast_data = multi_campaign(forecast_data,api_camp);
```

```
   tf = (length(years)-1)*api_camp; %define number of timeframes
   time_length = round(365/api_camp); %how much time is each timeframe **decimals are
acceptable
   if time_length*api_camp > 365
      time_length = time_length - 1; %handles drift from rounding up
   end
   years = zeros(1,1+tf);
   for b = 2:length(years)
      years(1,b) = years(1,b-1) + time_length;
   end
end

%define at what time an order needs to be placed based on the lead times
%and the year in which the material is required.
int_offset = manf_api + LT_int;
PO_int = []; %create a matrix that will be filled in with the purchase
          %order data
PO_api = []; %holding matrix for API POs
cum_int = [];
cum_api = [];
index_limits = size(forecast_data);
%need to initialize the demand year index to the first demand year that an
%order can be placed for
for j = 1:length(years)
   if years(j) >= int_offset
      demand_year = j;
      break
   end
end
%initialize current forecast to 1 so the time 0 version is the base
%forecast
current_forecast = 1;
%create the purchase order schedule for intermediates
while time < max_time
   if current_forecast <= index_limits(1)
      if time + int_offset == years(demand_year)
         volume = forecast_data(current_forecast,demand_year);
         PO_int =
vertcat(PO_int,[num2str(time),"A",num2str(volume),num2str(years(demand_year))]);
         cum_int =
vertcat(cum_int,[num2str(time),"","1",num2str(volume),num2str(years(demand_year))]);
         current_forecast = 1 + current_forecast; %move to next forecast version
         demand_year = demand_year + 1; %move to the next demand year
         time = time +1;
      elseif time > forecast_data(current_forecast,1)
         current_forecast = 1 + current_forecast;
```

```
        %this if loop checks the time in the simulation against the
        %forecast release date. If the simulation time is greater than
        %the forecast release date, it moves to the next forecast in
        %the future.
        time = time + 1; %move time counter forward one data
      else
        time = time +1;
      end
    else
      time = time +1;
    end
end

%%Create output matrices for intermediate
PO_dataI = vertcat(["Time","Name","Quantity","Demand Year"],PO_int);
cum_int = vertcat(["Time","Name","Quantity", "NumberCount","Demand Year"],cum_int);

    %%create the purchase order schedule for API
    %set variables to initial state
    time = 0;
    current_forecast = 1;
    demand_year = 0;
    for j = 1:length(years)
      if years(j) >= LT_api
        demand_year = j;
        break
      end
    end

    while time < max_time
      if current_forecast <= index_limits(1)
        if time + LT_api == years(demand_year)
          volume = forecast_data(current_forecast,demand_year);
          PO_api =
vertcat(PO_api,[num2str(time),"A",num2str(volume),num2str(years(demand_year))]);
          cum_api = vertcat(cum_api,[num2str(years(demand_year)-
manf_api),"","1",num2str(volume),num2str(years(demand_year))]);
          current_forecast = 1 + current_forecast; %move to next forecast version
          demand_year = demand_year + 1; %move to the next demand year
          time = time +1;
        elseif time > forecast_data(current_forecast,1)
          current_forecast = 1 + current_forecast;
          %this if loop checks the time in the simulation against the
          %forecast release date. If the simulation time is greater than
          %the forecast release date, it moves to the next forecast in
          %the future.
```

```
            time = time + 1; %move time counter forward one data
        else
            time = time +1;
        end
    else
        time = time +1;
    end
end

%%Create API matrix function outputs
PO_dataA = vertcat(["Time","Name","Quantity","Demand Year"],PO_api);
K = size(cum_api);
for i = 1:K(1)
    first_int_order = str2double(PO_dataA(2,4))
    cum_api(i,5)
    if first_int_order > str2double(cum_api(i,5))
    else
        cum_api = cum_api(i:end,:);
        break
    end
end


cum_api = vertcat(["Time","Name","Quantity", "NumberCount","Demand Year"],cum_api);
```

---

```
%Function: flex_volume.m
%Input:    simulation input file
%Purpose:  generate a purchase order schedule and volume commitment
%          tracking timeline

%this function generates a purchase order schedule with associated planning
%lead times for a flexible ordering model. A flexible ordering model is
%defined as one where a percentage of the demand is committed to at defined
%intervals.

%Notes
    %Units:  time [days]   volume [kgs]
    %LT = lead time

function [PO_dataI, PO_dataA, cum_int,cum_api] = flex_volume(file)
%bring in forecast and supply chain design parameters
    forecast_data = table2array(readtable(file,'Sheet','Forecast_Data'));
    parameters = readtable(file,'Sheet','Parameters_flexi');
```

```
%initialize the variables from the input file (parameters)
manf_rsm = table2array(parameters(1,2));
manf_int = table2array(parameters(2,2));
manf_api = table2array(parameters(3,2));
FreezeA_LT = table2array(parameters(4,2));
FreezeA_percent = table2array(parameters(5,2));
FreezeB_LT = table2array(parameters(6,2));
FreezeB_percent = table2array(parameters(7,2));
FreezeC_LT = table2array(parameters(8,2));
FreezeC_percent = table2array(parameters(9,2));

%the flexible model has 3 ordering points which are defined by the lead
%time from when it is on order should be available for use in the next
%stage - NOT until manufacturing starts - and the percentage of the
%total forecasted volume that is fixed at that point. This model builds
%volumes - there is currently no reduction built in.
seq = [];
cum_int = [];

PO_intA = []; %time of order, volume, demand year, freeze LT
PO_intB = [];
PO_intC = [];

%initialize all other variables
time = 0;
current_forecast = 1;
index_limits = size(forecast_data);
max_time = 1825;
years = [0 0 365 730 1095 1460 1825 2190 2555 2920 3285]; %represents 2016 to 2025
%generate the intermediate purchase orders. needs to included an
%additional offset to account for the API manufacturing time

%%
%generate type A Purchase Orders
for j = 1:length(years)
   if years(j) >= (FreezeA_LT + manf_api)
      demand_yearA = j;
      break
   end
end
while time < max_time
   if current_forecast <= index_limits(1)
      if time + FreezeA_LT + manf_api == years(demand_yearA)
         volume = FreezeA_percent*forecast_data(current_forecast,demand_yearA);
         PO_intA = vertcat(PO_intA,[time,volume,years(demand_yearA)]);
```

```
        seq = vertcat(seq, [num2str(time),"A", num2str(years(demand_yearA))]);
        cum_int = vertcat(cum_int,[years(demand_yearA), volume]);
        current_forecast = 1 + current_forecast; %move to next forecast version
        demand_yearA = demand_yearA + 1; %move to the next demand year
        time = time + 1;
      elseif time > forecast_data(current_forecast,1)
        current_forecast = 1 + current_forecast;
        %this if loop checks the time in the simulation against the
        %forecast release date. If the simulation time is greater than
        %the forecast release date, it moves to the next forecast in
        %the future.
        time = time + 1; %move time counter forward one data
      else
        time = time +1;
      end
    else
      time = time +1;
    end
end

%%
%generate type B Purchase Orders
%reinitialize variable
time = 0;
current_forecast = 1;
for j = 1:length(years)
    if years(j) >= (FreezeB_LT + manf_api)
        demand_yearB = j;
        break
    end
end
while time < max_time
    if current_forecast <= index_limits(1)
        if time + FreezeB_LT + manf_api == years(demand_yearB)
            net_volume = FreezeB_percent*forecast_data(current_forecast,demand_yearB);
            m = size(cum_int);
            for i = 1:m(1)
                if cum_int(i,1)== years(demand_yearB)
                    on_order = cum_int(i,2);
                    volume = net_volume - on_order;
                end
                if volume <= 0
                    volume = 0;
                end
            end
            PO_intB = vertcat(PO_intB,[time,volume,years(demand_yearB)]);
```

```
        seq = vertcat(seq, [num2str(time),"B", num2str(years(demand_yearB))]);
        for i = 1:m(1)
          if cum_int(i,1) == years(demand_yearB)
            cum_int(i,2) = cum_int(i,2) + volume;
          end
        end
        current_forecast = 1 + current_forecast; %move to next forecast version
        demand_yearB = demand_yearB + 1; %move to the next demand year
        time = time + 1;
      elseif time > forecast_data(current_forecast,1)
        current_forecast = 1 + current_forecast;
        %this if loop checks the time in the simulation against the
        %forecast release date. If the simulation time is greater than
        %the forecast release date, it moves to the next forecast in
        %the future.
        time = time + 1; %move time counter forward one data
      else
        time = time +1;
      end
    else
      time = time +1;
    end
end

%%
%generate type C Purchase Orders
%reinitialize variable
time = 0;
current_forecast = 1;
volume = 0;
for j = 1:length(years)
    if years(j) >= (FreezeC_LT + manf_api)
      demand_yearC = j;
      break
    end
end
while time < max_time
    if current_forecast <= index_limits(1)
      if time + FreezeC_LT + manf_api == years(demand_yearC)
        net_volume = FreezeC_percent*forecast_data(current_forecast,demand_yearC);
        m = size(cum_int);
        for i = 1:m(1)
          if cum_int(i,1)== years(demand_yearC)
            on_order = cum_int(i,2);
            volume = net_volume - on_order;
            if volume < 0
```

```
                volume = 0;
            end
        end
    end
    PO_intC = vertcat(PO_intC,[time,volume,years(demand_yearC)]);
    seq = vertcat(seq, [num2str(time),"C", num2str(years(demand_yearC))]);
    for i = 1:m(1)
        if cum_int(i,1) == years(demand_yearC)
            cum_int(i,2) = cum_int(i,2) + volume;
        end
    end
    current_forecast = 1 + current_forecast; %move to next forecast version
    demand_yearC = demand_yearC + 1; %move to the next demand year
    time = time + 1;
elseif time > forecast_data(current_forecast,1)
    current_forecast = 1 + current_forecast;
    %this if loop checks the time in the simulation against the
    %forecast release date. If the simulation time is greater than
    %the forecast release date, it moves to the next forecast in
    %the future.
    time = time + 1; %move time counter forward one data
else
    time = time +1;
end
else
    time = time +1;
end
end

%% Create the order schedule for intermediates
PO_scheduleI = sortrows(seq,[1 3])
%add column labels
PO_scheduleI = vertcat(["Time(days)","Order Leadtime(days)","Demand
Year"],PO_scheduleI);
PO_combinedI = sortrows(vertcat(PO_intA,PO_intB,PO_intC),[1 3])
%add column labels
PO_combinedI = vertcat(["Time(days)","Order Qty(kg)","Demand Year"],PO_combinedI);
%combine the data into a single array that is organized as such
%[time, order Type, demand year, order quantity, cum qty for demand year]
PO_dataI = horzcat(PO_scheduleI(:,1:2),PO_combinedI(:,2:3));

%% API PURCHASE ORDER SCHEDULE
%Now find the purchase order schedule for API
%reset the sequence to a null and define api cumulative volumes
seq = [];
cum_api = [];
```

```
PO_apiA = []; %time of order, volume, demand year, freeze LT
PO_apiB = [];
PO_apiC = [];

%initialize all other variables
time = 0;
current_forecast = 1;
index_limits = size(forecast_data);
max_time = 1825;
years = [0 0 365 730 1095 1460 1825 2190 2555 2920 3285]; %represents 2016 to 2025
%generate the intermediate purchase orders. needs to included an
%additional offset to account for the API manufacturing time

%%
%generate type A Purchase Orders
for j = 1:length(years)
   if years(j) >= (FreezeA_LT)
      demand_yearA = j;
      break
   end
end
while time < max_time
   if current_forecast <= index_limits(1)
      if time + FreezeA_LT == years(demand_yearA)
         volume = FreezeA_percent*forecast_data(current_forecast,demand_yearA);
         PO_apiA = vertcat(PO_apiA,[time,volume,years(demand_yearA)]);
         seq = vertcat(seq, [num2str(time),"A", num2str(years(demand_yearA))]);
         cum_api = vertcat(cum_api,[years(demand_yearA), volume]);
         current_forecast = 1 + current_forecast; %move to next forecast version
         demand_yearA = demand_yearA + 1; %move to the next demand year
         time = time + 1;
      elseif time > forecast_data(current_forecast,1)
         current_forecast = 1 + current_forecast;
         %this if loop checks the time in the simulation against the
         %forecast release date. If the simulation time is greater than
         %the forecast release date, it moves to the next forecast in
         %the future.
         time = time + 1; %move time counter forward one data
      else
         time = time +1;
      end
   else
      time = time +1;
   end
end
```

```
%%
%generate type B Purchase Orders
%reinitialize variable
time = 0;
current_forecast = 1;
for j = 1:length(years)
   if years(j) >= (FreezeB_LT)
      demand_yearB = j;
      break
   end
end
while time < max_time
   if current_forecast <= index_limits(1)
      if time + FreezeB_LT == years(demand_yearB)
         net_volume = FreezeB_percent*forecast_data(current_forecast,demand_yearB);
         m = size(cum_api);
         for i = 1:m(1)
            if cum_api(i,1)== years(demand_yearB)
               on_order = cum_api(i,2);
               volume = net_volume - on_order;
            end
            if volume <= 0
               volume = 0;
            end
         end
         PO_apiB = vertcat(PO_apiB,[time,volume,years(demand_yearB)]);
         seq = vertcat(seq, [num2str(time),"B", num2str(years(demand_yearA))]);
         for i = 1:m(1)
            if cum_api(i,1) == years(demand_yearB)
               cum_api(i,2) = cum_api(i,2) + volume;
            end
         end
         current_forecast = 1 + current_forecast; %move to next forecast version
         demand_yearB = demand_yearB + 1; %move to the next demand year
         time = time + 1;
      elseif time > forecast_data(current_forecast,1)
         current_forecast = 1 + current_forecast;
         %this if loop checks the time in the simulation against the
         %forecast release date. If the simulation time is greater than
         %the forecast release date, it moves to the next forecast in
         %the future.
         time = time + 1; %move time counter forward one data
      else
         time = time +1;
      end
   else
```

```
        time = time +1;
    end
end

%%
%generate type C Purchase Orders
%reinitialize variable
time = 0;
current_forecast = 1;
volume = 0;
for j = 1:length(years)
    if years(j) >= (FreezeC_LT)
        demand_yearC = j;
        break
    end
end
count = 0;
while time < max_time
    if current_forecast <= index_limits(1)
        if time + FreezeC_LT== years(demand_yearC)
            net_volume = FreezeC_percent*forecast_data(current_forecast,demand_yearC);
            m = size(cum_api);
            for i = 1:m(1)
                if cum_api(i,1)== years(demand_yearC)
                    on_order = cum_api(i,2);
                    volume = net_volume - on_order;
                    if volume < 0
                        volume = 0;
                    end
                end
            end
            PO_apiC = vertcat(PO_apiC,[time,volume,years(demand_yearC)]);
            seq = vertcat(seq, [num2str(time),"C", num2str(years(demand_yearA))]);
            for i = 1:m(1)
                if cum_api(i,1) == years(demand_yearB)
                    cum_api(i,2) = cum_api(i,2) + volume;
                end
            end
            current_forecast = 1 + current_forecast; %move to next forecast version
            demand_yearC = demand_yearC + 1; %move to the next demand year
            time = time + 1;
        elseif time > forecast_data(current_forecast,1)
            current_forecast = 1 + current_forecast;
            %this if loop checks the time in the simulation against the
            %forecast release date. If the simulation time is greater than
            %the forecast release date, it moves to the next forecast in
```

```
            %the future.
            time = time + 1; %move time counter forward one data
        else
            time = time +1;
        end
    else
        time = time +1;
    end
end
%% Create the order schedule for API
PO_scheduleA = sortrows(seq,[1 3]);
%add column labels
PO_scheduleA = vertcat(["Time(days)","Order Lead Time(days)","Demand
Year"],PO_scheduleA);
PO_combinedA = sortrows(vertcat(PO_apiA,PO_apiB,PO_apiC),[1 3]);
%add column labels
PO_combinedA = vertcat(["Time(days)","Order Qty(kg)","Demand Year"],PO_combinedA);
%combine the data into a single array that is organized as such
%[time, order Type, demand year, order quantity, cum qty for demand year]
PO_dataA = horzcat(PO_scheduleA(:,1:2),PO_combinedA(:,2:3));
%create a release time for the cumulative API
cum_api = horzcat(cum_api,cum_api(:,1));
syntax = []; %this is a matrix that will be filled to get the correct formating for the input into
the sim model
for h = 1:length(cum_api)
    cum_api(h,1) = cum_api(h,1) - manf_api;
    syntax = vertcat(syntax,[0,1]);
end
cum_api = horzcat(cum_api(:,1),syntax,cum_api(:,2:3));
cum_api = vertcat(["Release Time(days)", "Name","Quantity","Volume","Demand
Year"],cum_api);
```

## References


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