Machine Learning and Stochastic Simulation for Inventory Management

by

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Abstract

This thesis explores the use of advanced data-driven techniques for dimensioning safety stock and optimizing inventory in a supply chain. The thesis is based on data and insights for raw material inventory at Amgen, a biotech company. Resilient inventory management is important in the biopharma and biotech sector as the repercussions of a drug shortage are dire. However, the complexity of biomanufacturing processes creates significant variability and uncertainty around lead times and demand. Amgen currently holds high raw material inventories across thousands of materials to mitigate risks of stockouts that could delay production. However, the policies of holding high raw material inventories in Amgen have resulted in increased holding costs and also tied up working capital.

To address this challenge and find a sustainable method for managing raw materials in the company and by extension, other stages of production, a novel methodology is developed. Machine learning models such as CatBoost, Extreme Gradient Boosting (XGBoost) and Random Forest are proposed to forecast lead times and demand. The models are trained on datasets of 10,000+ materials, incorporating unique patterns based on factors like suppliers' historical delivery performance, historical demand pattern and material characteristics. A segmentation framework is also developed to properly allocate service levels based on risk tolerance for different category of materials. Stochastic simulation then applies the learned predictive distributions to quantify optimal safety stock levels under uncertainties. This considers desired service levels, holding costs, risk tolerance, cost-risk tradeoffs and potential disruptions in what-if scenario cases to support resilience.

The methodology is validated on sample materials with both short and long lead times. Results indicate potential inventory reductions of over 25% while still preventing stockouts, enabling multimillion dollar savings in procurement and holding costs. A phased implementation plan is also proposed in order to ensure smooth transition using this new data-driven approach in the organisation, taking into consideration change management.

This solution fuses predictive analytics with simulation and optimization to transform safety stock calculation from a cost burden to a competitive advantage. The dynamic data-driven framework significantly enhances supply chain resilience and efficiency in the vitally important biopharmaceutical industry, where patient outcomes are at stake. The methodologies developed could be applied across various production stages and tailored to other sectors.

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Contents

List of Figures

List of Tables

Acronyms

ARIMA autoregressive integrated moving average. 37

BOM bill of materials. 17, 70

CatBoost categorical boosting. 35, 69

DP drug product. 16

DS drug substance. 16

FDP finished drug product. 16

GMP Good Manufacturing Practice. 18

IoT Internet of Things. 38

LightGBM light gradient boosting machine. 35, 69

MAE Mean Absolute Error. 35

MAPE mean absolute percentage error. 73

MFC months forward coverage. 22, 23

MSE Mean Squared Error. 36

OTD on-time delivery rate. 20

RMSE Root Mean Squared Error. 36

SLAs Service Level Agreements. 42

SRM Supplier Relationship Management. 41

SS safety stock. 22

VMI Vendor-Managed Inventory. 42

XGBoost extreme gradient boosting. 35, 69

Chapter 1

Introduction

This thesis explores techniques for optimizing inventory and determining safety stock levels in the biopharmaceutical supply chain. Chapter 1 provides background on the importance of effective inventory management in the biopharmaceutical industry and outlines the key challenges Amgen faces regarding demand variability, production defects and supplier performance. Chapter 2 extensively reviews relevant literature on common inventory management methods, inventory segmentation, safety stock dimensioning, demand and lead time forecasting and supply chain resilience strategies. The chapter also discusses different quantitative and qualitative forecasting methods along with their benefits and limitations. Chapter 3 delineates the proposed data-driven methodology for enhanced safety stock determination, leveraging machine learning models for demand and lead time forecasting. The disruption simulation framework for managing risks and what-if scenarios is also discussed. Chapter 4 demonstrates implementation results for sample materials, validating the business value of the approach. The limitations of the proposed approach are also discussed in this chapter. Finally, Chapter 5 proposes an operational roadmap for translating the models into organizational improvements through change management, alignment, and monitoring. This chapter also discusses further improvement opportunities on the proposed methodology and Amgen's inventory management operations.

1.1 Background and Project Importance

Efficient inventory and supply chain management is critical in the biopharmaceutical industry to help improve new drug development pipelines and timelines. The biopharma industry faces challenges of lengthy and costly R&D processes, with average new drug approval taking 6-9 years and over $1 billion [9]. New drug approvals have decreased in recent decades, falling from 45 approved in 1996 to just 21 in 2010 [9]. Inventory and supply chain optimization can help address these inefficiencies. For example, improving inventory availability of needed research supplies, chemicals, and equipment can help accelerate R&D timelines. Enhancing supply chain coordination with contract manufacturers can get new drugs to market faster post-approval. With biopharma companies often operating at a loss during the R&D phase, inventory and supply chain improvements that reduce costs and increase pipeline throughput can provide major competitive advantages. This can ultimately enable more new drugs to reach patients in need. Thus, supply chain and inventory management plays a pivotal role in supporting the growth and viability of the high-potential yet high-risk biopharmaceutical industry.

Biopharmaceutical companies face major challenges in aligning capacity to uncertain demand when designing their supply chains [78]. At the operation stage, responsiveness is a typical challenge. Most pharmaceutical products involve multi-stage production with a usual supply lead time of 300 days [78]. Implementing supply chain optimization techniques such as debottlenecking and decoupling, in tandem with coordinated inventory management, is essential for agile responses to shifting market conditions. Additionally, a strong comprehension of the key factors influencing supply chain flows allows for more targeted and impactful strategies.

Amgen has about 27 finished drug product (FDP) [7] lines manufactured in eight manufacturing plants [69] which are distributed globally. Thousands of raw materials are required to manufacture and package these FDPs and these raw materials are sourced from hundreds of manufacturers and suppliers. There are three critical drug manufacturing stages in the Amgen drug manufacturing process. They are drug substance (DS), drug product (DP) and finished drug product (FDP). The production flow is shown in Figure 1-1.

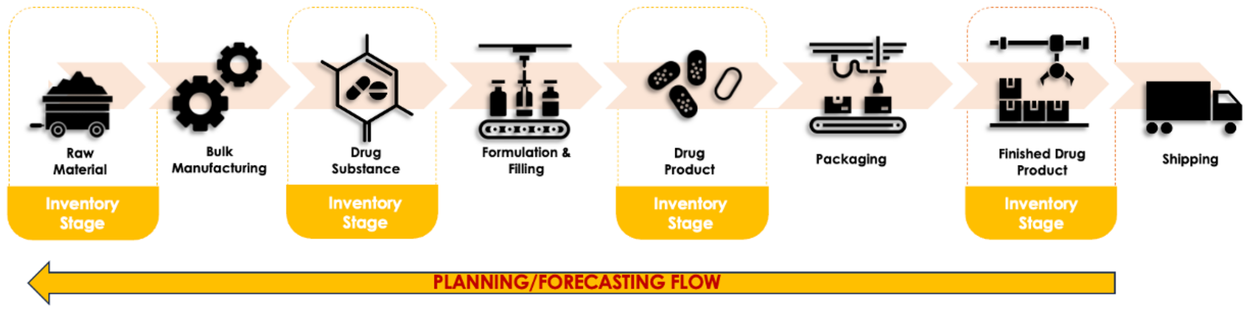

Figure 1-1: Product Flow and Different Inventory Stages at Amgen

Amgen, as with other organisations across several industries, uses a top down approach to determine raw material inventory. In order to plan production of these finished drug products (FDP), the commercial and planning team forecasts sales of the finished drug products based on commercial signals and historical sales, using tools called Anaplan [29] and Hyperion [64]. These finished drug product forecasts are used to create bill of materials (BOM) to plan the raw materials requirement for each month and period. There are also some raw materials that are used in the production and packaging process such gloves, distribution packaging, process support. These raw materials are regarded to as non-bill of materials (BOM) category because their demand plan is not directly derived from the Finished Drug Product Forecast. The future demand plan of these materials are estimated using their historical consumption and do not have a direct connection to the FDP forecast.

There are three types of manufacturing inventories: "raw materials, work in process and finished goods" [60]. The flow chart in Figure 1-1 shows how the planning process is currently being done at Amgen and the inventory stages.

There are 10,000+ raw materials in Amgen's raw material inventory portfolio. All the raw materials are classified into 13 major categories, with eight categories being BOM and 5 Non-BOM. The different category of raw materials required for production and included in the scope of this project are shown in Table 1.1.

The percentage composition of the number of unique raw materials in each material category is shown in Figure 1-2. It is important to note that several raw materials are used in multiple manufacturing plants in the network.

Due to the critical nature of the products being manufactured by Amgen, it is important

BOM Categories	
GM0100	Good Manufacturing Practice (GMP) Chemicals (also has Non-BOM items)
GM0200	Containers (also has Non-BOM items)
GM0300	Devices
GM0600	Filters (also has Non-BOM items)
GM0700	Tubing (also has Non-BOM items)
GM0800	Primary Packaging Components
GM1000	Resin
GM1100	Serum/Media (also has Non-BOM items)
Non-BOM Categories	
GM0400	Distribution Packaging
GM0500	GMP Apparel
GM0900	Secondary Packaging Components
GM1300	Non-Critical Chemicals
GM1400	Process Support

Table 1.1: BOM and Non-BOM Categories of Raw Materials

that the stock out risk is reduced and there are enough raw materials to satisfy customer demand at every point in time. However, the demand of the products required by the customer is constantly fluctuating, influenced by external factors such as competition, consumer needs etc., and this affects the demand of the raw materials. Some of these unforeseen fluctuations in demand are managed by the safety stock that the company holds; however, the company is currently faced with the dilemma of how much more to hold and if their current safety stock policies are robust enough or too conservative, risking holding up working capital and requiring additional warehouse space.

The demand plan for the raw materials is also dependent on the demand plan of the finished drug product, and variability in the FDP forecast also affects the raw material plan. Therefore, the challenge is knowing how much safety stock to hold such that one does not hold too much or too little.

1.2 Problem Statement

Raw material inventory levels have been climbing at Amgen and the company is currently holding circa $1 textbillion [16] worth of raw material inventory, across all its plants and sites, with an opportunity to optimize inventory. Amgen's mantra "Every Patient, Every

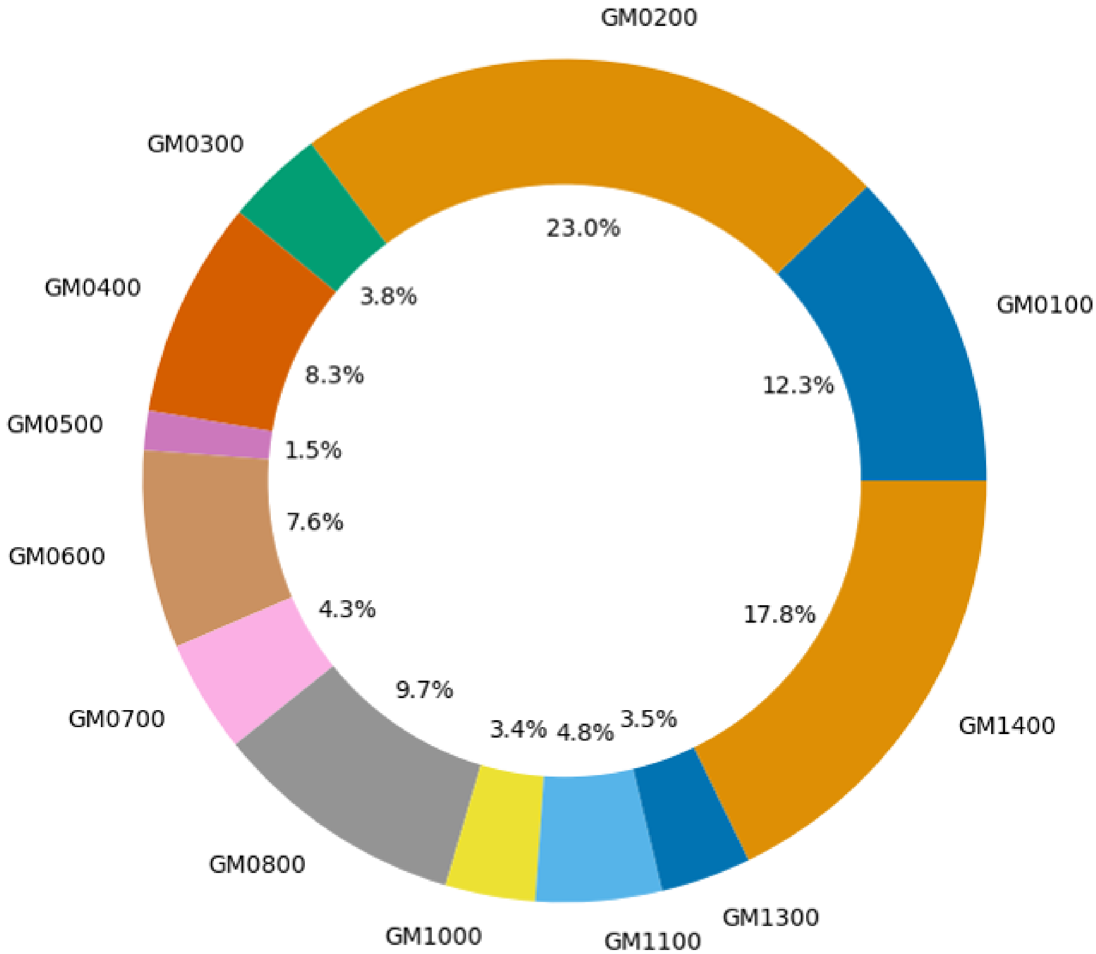

Figure 1-2: Raw Material Percentage Composition by Material Category

Time" [79] requires that the company does not stock out of raw material inventory to serve patients. However, inventory holding costs have increased, and long lead times coupled with demand variability have resulted in expiry and scrap risk. There is an opportunity to reduce on-hand inventory while managing non-uniformly distributed demand, lead time variability, production and material defects, supply risk and variability, holding cost, and expiry risk and ensure that there is a standardized and sustainable way to live up to that mantra.

The following are some of the reasons why Amgen has held a lot of inventory so far.

1. **Demand and Production Schedule Variability:** The company has a top-down policy of creating the demand plan from the FDP forecast. As a result, the demand

plan for most raw materials (BOM) is highly dependent on the forecast of the finished drug product (FDP) and the accuracy of those forecasts. Therefore, variability in the FDP forecast also affects the raw material plan. The challenge here is the FDP production is based on the internal production schedule in which the company can make adjustments, whereas for the raw materials required to manufacture the finished drug products, the availability is based on the supplier lead times and supply plan. Due to the different lead times for the raw materials and the fact that the supplier plan and response rate is not completely within Amgen's control, the company has historically held an amount of safety stock to account for such unforeseen or unplanned variability in demand that cannot be mitigated quickly due to the lead time constraints.

2. **Production and Material Defects:** The production process in the drug manufacturing plant is very delicate, and due to the high levels of quality required for products produced in these facilities, whenever a batch is contaminated, a new batch of raw materials needs to be requisitioned from the warehouse to fulfill the production plan. This affects the target inventory levels of the raw materials. Additionally, while Amgen has quality controls in place to confirm the quality of raw materials when they are delivered by suppliers, sometimes, during production, some raw materials can be observed as defective, affecting the inventory levels.

3. **Supplier Performance and Supply Planning:** The historical performance of the suppliers have been variable due to several factors, including the supply planning at Amgen. The supply planning team sometimes places orders early, which can be deemed as good, and late, which would definitely impact the lead time of the supplier and subsequently the supply of a raw material. An analysis of orders placed from January 2016 to June 2023 was done on orders placed on time by Amgen, and this showed that suppliers had an on-time delivery rate of 58.27%. Contextualizing orders placed before COVID (January 2016 to January 2020), the on-time delivery rate was 55.39% and post COVID (January 2020 till date) was about 60.86%. This demonstrates that even before supply chain disruptions, some suppliers had variability in lead times. The on-time delivery rate (OTD) was measured as the percentage of deliveries that meet or precede

the planned delivery time.

Additionally, the agreed delivery times have been changing over the years for some suppliers due to several factors, such as capacity, competition, and others. An example of this is shown in Figure 1-3 where the planned/agreed lead times have changed from order to order for Vendor Z for orders placed for a particular material.

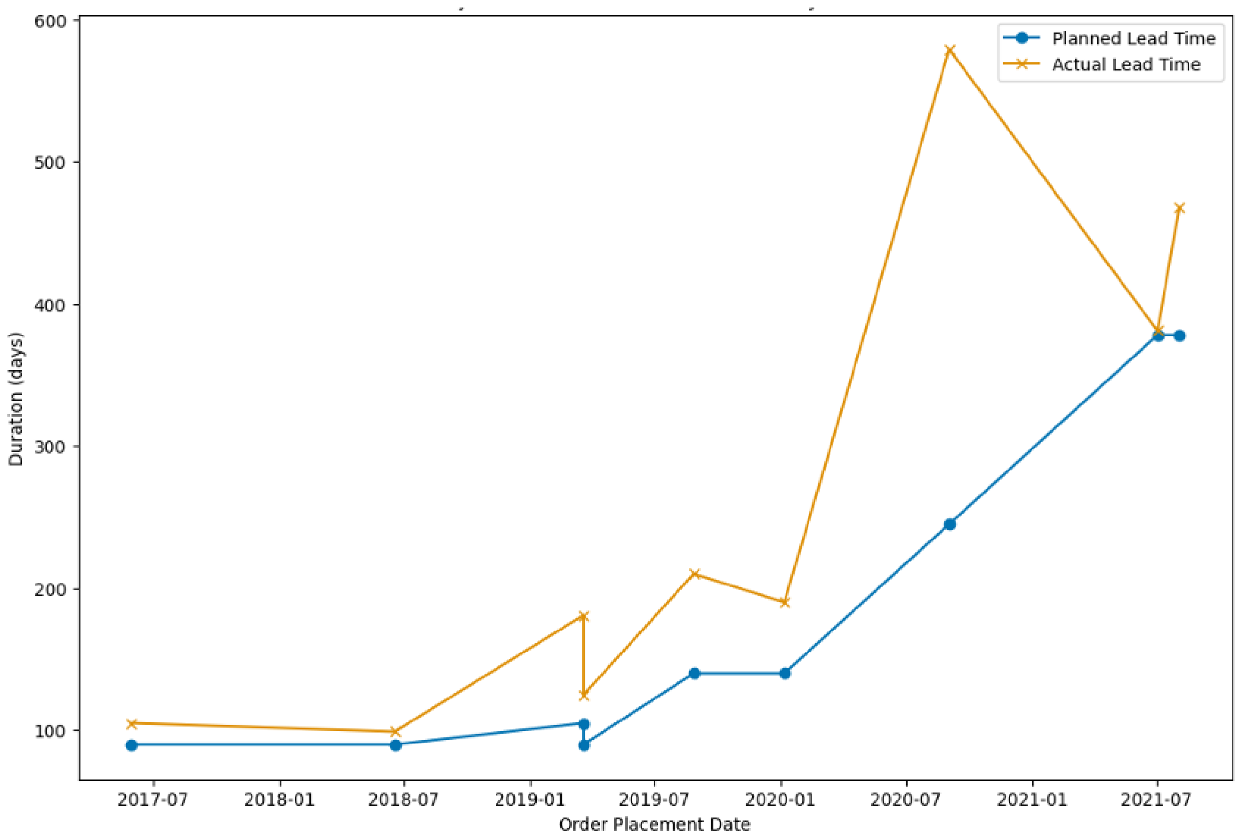

Figure 1-3: Delivery Time Variation for Material X to Plant Y Supplied by Vendor Z

Also, before the pandemic, the actual lead times were very variable, similar to after the pandemic, as depicted in Figure 1-4.

4. **Supply Chain Disruptions and Impact of the Pandemic:** The advent of the pandemic caused significant supply chain disruptions, resulting in a global supply chain challenge that companies are still addressing. As illustrated in Figure 1-3, orders placed after 2020, when the pandemic started with that vendor, showed that the actual lead times were significantly higher than the agreed lead times. Lead times have become significantly variable, as also indicated in Figure 1-4.

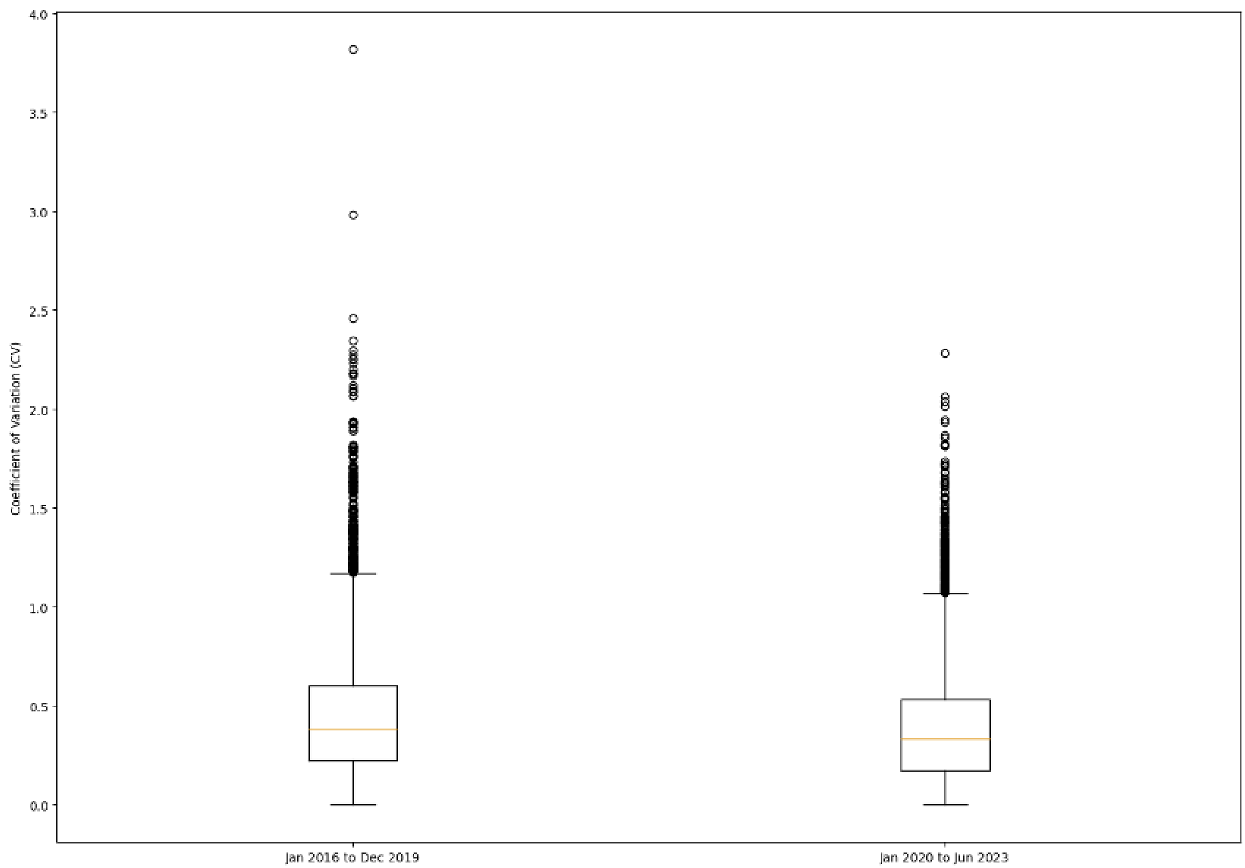

Figure 1-4: Coefficient of Variation of Lead Times Pre and Post COVID

Inventory levels have also been influenced by the company's conservative response to supply chain disruptions and performance. There are raw materials with highly variable demand.

5. **Amgen's Safety Stock Policy:** The company uses a months forward coverage (MFC) policy to calculate how much safety stock needs to be held every month. This determines the extra inventory kept on hand. Months forward coverage (MFC) involves setting a minimum number of months for future demand coverage and adding that to equate to safety stock for the present month. The current safety stock (SS) policies are manually set, site-specific, and can have multiple "de-coupled" layers. The safety stock months forward coverage policy is presented in Equation 1.1.

$$
\begin{aligned}
\text{Total Safety Stock} = &\ \text{Minimum MFC (set target)} \\
&+ \text{Buffer (Minimum quantity)} \\
&+ \text{Site Specific additional SS}
\end{aligned} \tag{1.1}
$$

The minimum MFC is based on static off-line risk groupings. The buffer is static, determined by sites, not standardized, and not coupled with MFC setting. The site-specific additional safety stock is also determined by sites, not standardized, and not integrated with other SS factors.

The MFC policy is simple and flexible, and when set as high as possible, it allows for surplus inventory to mitigate certain risks. However, this policy does not broadly correlate with lead time and risk profile, which significantly influences inventory level. It does not account for the non-normal demand distribution of certain materials, promotes obsolescence which leads to potential high sunk costs, and results in high inventory costs and tied-up working capital.

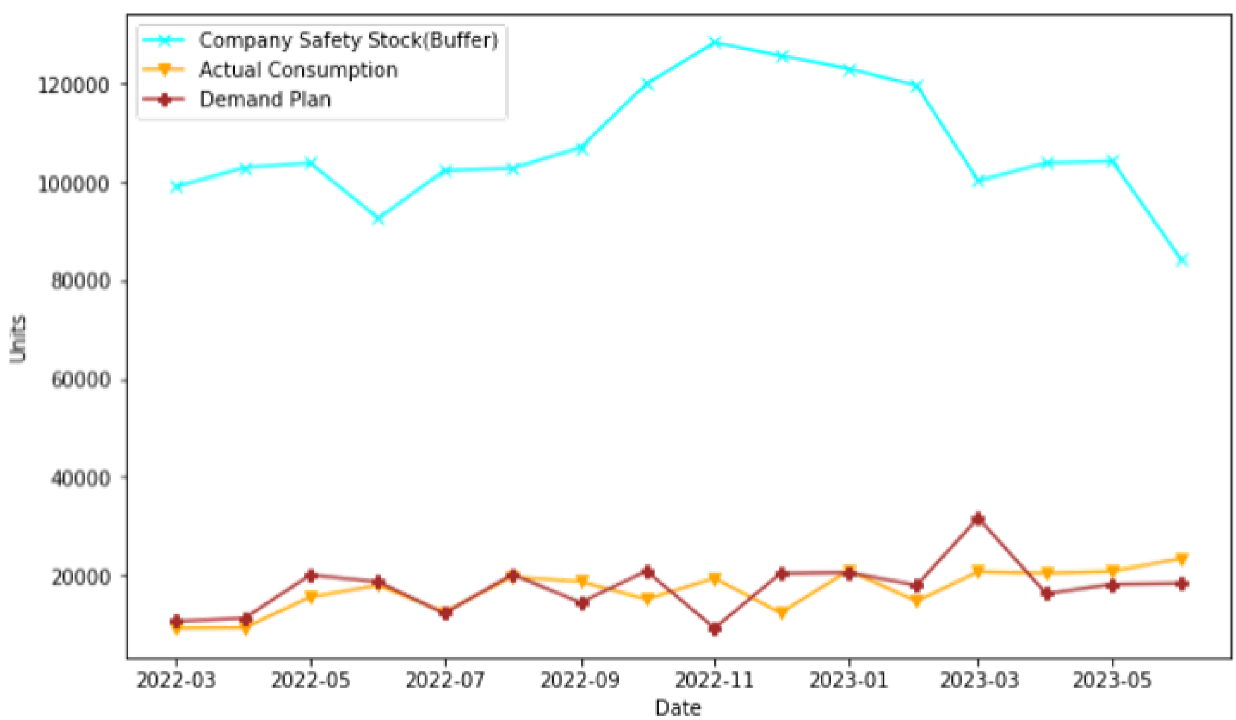

Figure 1-5: Demand, Safety Stock and Actual Consumption for a sample material

For instance, in Figure 1-5, a raw material has a lead time of 40 days, indicating a short response time. Nevertheless, the company holds safety stock six times the demand, illustrating that the safety stock policy set by the company does not correlate with the lead time risk profile of this raw material. However, some materials may have other strategic factors or supplier risks at play, or deficiencies in data accuracy, making it difficult to simply and broadly reduce inventory targets.

This safety stock policy, combined with all the sources of variability and risk highlighted above, has influenced Amgen to maintain high inventory stock levels for raw materials.

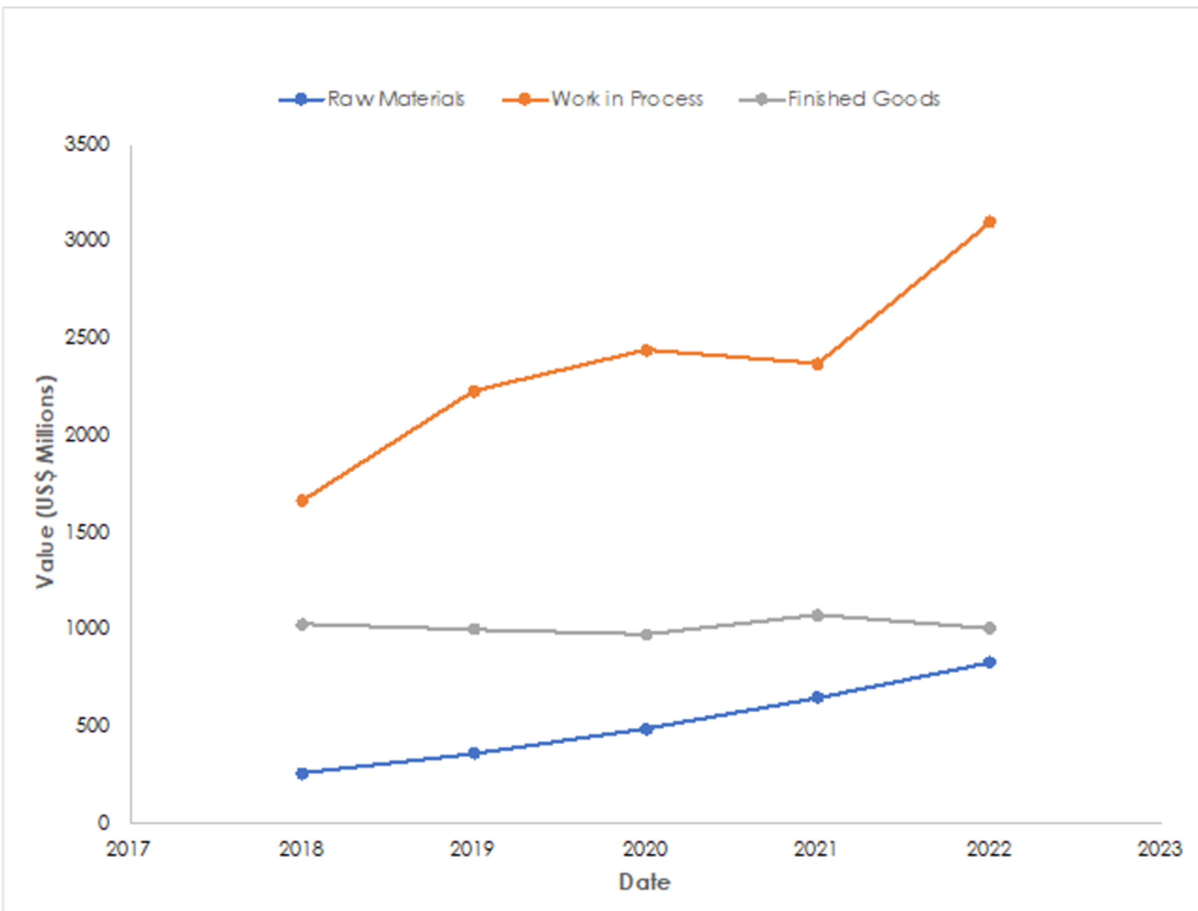

Figure 1-6: Amgen Inventory Value from 2018 to 2022 [14] [15] [16]

In Figure 1-6, the raw material and work-in-process inventory values have been increasing year on year from 2018 until now. In contrast, the finished drug product value has remained fairly consistent. This reflects the conservative approach the organization has taken concerning target inventory levels and safety stock policies. Note that the figure is not adjusted for growth in FDP stock keeping units (SKUs) over the same period, which also tend to drive inventory up.

The following chapters delineate in detail supply chain and safety stock challenges in the biotechnology industry, the proposed methodology to manage Amgen's inventory and safety stock policy, and other future improvements that could be made in Amgen's operations.

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Chapter 2

Review of Key Concepts

The biotechnology sector presents unique challenges for supply chain management due to the specific nature of its products and processes. In particular, accurately forecasting demand, anticipating lead times, and determining appropriate safety stock levels are pivotal in ensuring that supply chains are both efficient and responsive. With advancements in computational techniques such as machine and deep learning, there are new opportunities to enhance these traditional inventory management practices. The review of concepts provided in this chapter examines the integration of data-driven techniques into the biotechnology supply chain, focusing on their practical implications, advantages, and potential limitations. This chapter begins with a review of the challenges and methodologies involved in demand and lead forecasting, before delving into safety stock.

2.1 Demand Forecasting

Forecasting is an estimation of a particular variable or quantity over a specified future time period [5]. The role of demand forecasting is pivotal across various industries, serving not only in demand planning but also in enhancing inventory management and cost optimization [25]. Most organisations rely on the efficiency of demand forecasting to make critical decisions such as planning, capacity and resource management, etc. [5].

The current state of supply and demand imbalance has increased the volatility of many raw materials for production [60]. Real data has become ubiquitous and companies have abandoned the traditional inventory management and demand prediction approaches, and are turning to data-driven models because it is more efficient. Variance amplification poses a common challenge in multi-echelon supply chains, where distortion of demand information gets amplified as it passes through different stages. Research suggests that machine learning and other advanced forecasting techniques could help mitigate the variance amplification effect [35]. Forecasting demand is typically more difficult further upstream in the supply chain. Information fed through the chain often gets distorted as it passes between partners, compounding inaccuracies - an effect known as the bullwhip effect [35]. Advanced techniques that can model complex patterns in demand data could help reduce this distortion. By enhancing visibility and coordination through improved demand projections, supply chain efficiency and performance can be significantly improved [35].

The central goal involves minimizing deviations between projected and realized demand. The efficacy of the employed forecasting methodology is critical in ensuring the minimization of such deviations. Pronounced deviations in forecasts can have ripple effects on the overall supply chain. Demand forecasting has typically been performed via judgement and statistical means. Green et al. [40] categorizes these forecasting methodologies in Figure 2-1. It is a standard practice to employ a multifaceted approach to forecasting, acknowledging its nature as both an art and a science.

2.1.1 The Importance of Demand Forecasting

In today's rapidly evolving market environment, the ability to accurately forecast demand has become even more crucial. It not only serves as the backbone of effective supply chain management but also as a critical factor in maintaining competitive advantage. Below are key reasons highlighting the significance of demand forecasting:

- **The need for accuracy in planning**: Accurate demand planning is critical to supply chain management as it influences the ability of a company to balance supply with demand. Inaccuracy in demand can lead to operation challenges such as stock outs or overstock. Overstock results in increased inventory carrying costs and potential expiry risk, while stock outs can lead to lost sales and damage to customer relationships. Pre-

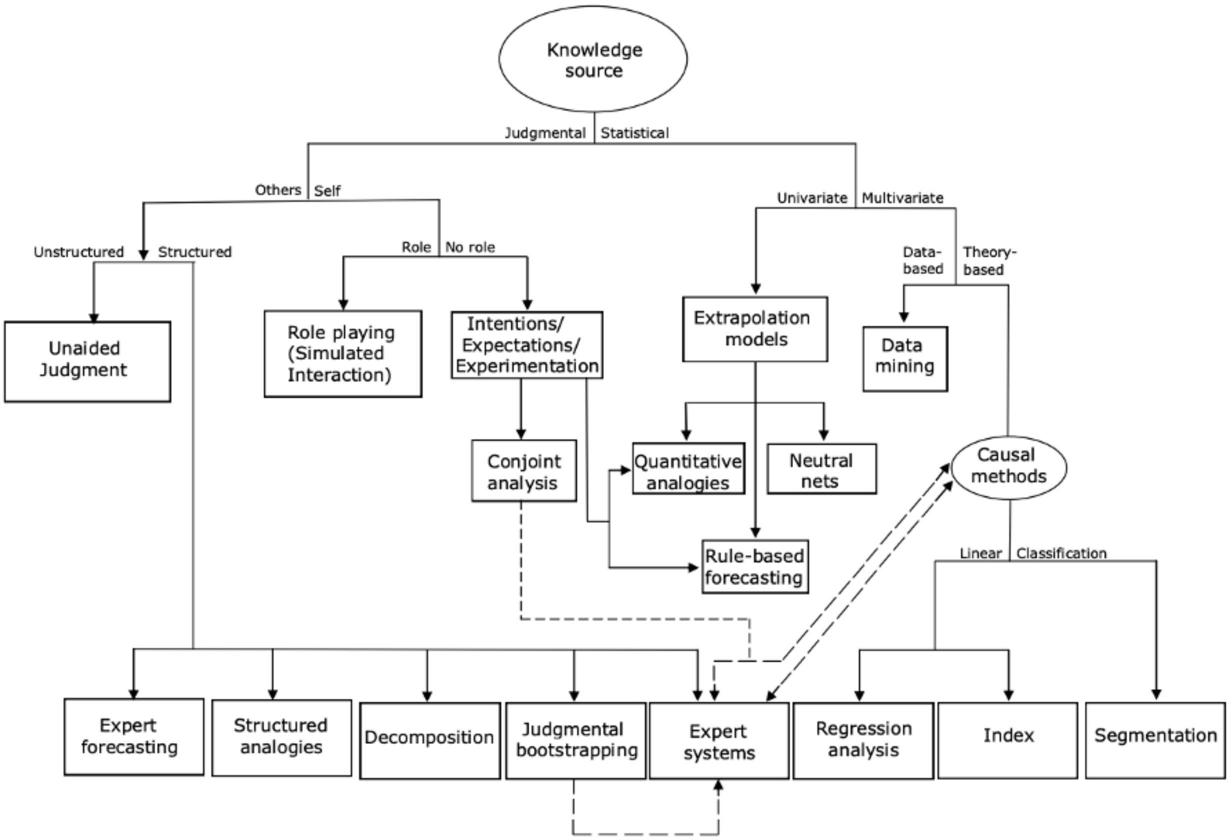

Figure 2-1: Methodology Tree for Forecasting [40]

cision in demand planning is also important to manage suppliers, inventory, production schedules and overall an efficient supply chain. Continuous monitoring and alignment of forecasts with actual demand data is essential to refine and enhance the accuracy of future predictions.

- **Dynamic market conditions**: Having precise demand forecasting is typically difficult due to the level of demand volatility and other uncertainties. Demand volatility is typically affected by endogenous and exogenous factors [3]. Such factors include market conditions, dynamic consumer behavior, discounts, etc. Demand volatility could cause stock outs and increased inventory costs, if demand forecasting is not as accurate as possible to take into account such volatility. The dynamic nature of market demand necessitates a rigorous, data-driven approach to demand forecasting, integrating historical sales data, market trends, and predictive analytics.

2.1.2 Traditional Approaches to Demand Forecasting

Traditional approaches to demand forecasting typically involve historical data analysis and various statistical methods. The typical traditional techniques have been segmented into qualitative and quantitative techniques, as summarised below.

Qualitative Techniques

Some of the common qualitative methods of traditional demand forecasting include:

- **Expert Judgement:** Expert judgement relies on the knowledge and intuition of experts to predict future demand. Experts may include industry professionals, sales personnel, or external consultants with deep understanding and insights into the market, products, and consumer behavior. Expert judgment is typically used in situations where there is limited data or dynamic market conditions [40]. It is often used in conjunction with other forecasting methods to improve reliability and accuracy. Industries like technology and pharmaceuticals where market conditions and consumer preferences can change rapidly tend to use this method of forecasting. Limitations of this method includes inconsistencies in perspectives, bias and over reliance on previous data or experiences.

- **Market Research:** Market research involves gathering and analyzing information directly related to consumer preferences and behaviors for a particular product or service. This method is typically used when historical data is insufficient or unavailable for new or existing products or services. However, it can be time consuming and costly and subject to individual biases [40].

- **Delphi Method:** Originating in the 1950s at the RAND Corporation, the Delphi technique has become a prominent methodology in facilitating forecasting and decision-making across diverse disciplines [74] [93] [41]."The Delphi Method is based on a structured process for collecting and distilling knowledge from a group of experts by means of a series of questionnaires interspersed with controlled opinion feedback" [41]. The context in which the Delphi method is to be applied is critical to deciding whether to use it or not. Key advantages of the Delphi method in demand forecasting include its ability to capture a wide range of expert opinions and its flexibility in addressing complex and uncertain market conditions. Experts can consider factors beyond what traditional statistical models may capture, such as emerging market trends, technological advancements, or socio-economic shifts. However, its effectiveness heavily depends on the selection of experts and their expertise in the relevant field. It can also be time-consuming and may require several rounds before reaching a consensus. The outcome of a Delphi sequence is based on opinions which are only as valid as the credibility of the experts who make up the panel [74] [93] [41].

Quantitative Time Series Analysis

Some of the common quantitative methods of traditional demand forecasting include:

- **Moving Averages:** One of the commonly used methods of time series forecasting is the moving average (MA) method, has many variations. Moving average methods are used to analyze time series data, primarily to smooth out short term fluctuations and reveal longer term patterns. Some of these variations include simple moving average (SMA), weighted moving average (WMA), and exponential moving average (EMA) [44]. SMA calculates the average of a selected range of previous data points in time series data. The WMA is a modified SMA with an adjustment that allocates higher weight values to more recent data than the older ones in a linear manner. EWMA helps to smooth random fluctuations by applying greater weights, similar to WMA but calculating the weighting factor using an exponential function [44]. Moving average methods are advantageous due to their simplicity and ease of implementation. However, they are inherently lagging indicators and may not accurately predict future trends, especially in volatile markets. They also do not account for any other variables that might affect the dependent variable, such as macroeconomic factors or seasonal variations.For example, Merkuryeva et al. [58] utilized an SMA method to forecast the demand for a pharmaceutical product and showed that the results were greatly influenced by recent data and could not properly account for historical data or possible future trends. In practice, moving average methods are often used in conjunction with other forecasting techniques to improve accuracy and reliability in predicting future trends [88].

- **Exponential Smoothing:** The core idea behind exponential smoothing is it assigns exponentially decreasing weights to past data and assigns the most recent data the highest weights [46]. It does this through a smoothing constant (alpha), which ranges between 0 and 1. A higher alpha gives more weight to recent data, making the method more responsive to changes, while a lower alpha makes the forecast more stable but less sensitive to recent changes. The equation for exponential smoothing is below [46]:

$$s_0 = x_0$$
$$S_t = \alpha x_t + (1 - \alpha)\, S_{t-1}, t > 0$$

where:

$$x_t = \text{observations}$$
$$t = \text{time}$$
$$\alpha = \text{smoothing factor}; 0 < \alpha < 1$$

The three main types of exponential smoothing are single exponential smoothing which is ideal for data with no clear trend or seasonality [85], double exponential smoothing which is ideal for data with trends, and triple exponential smoothing for data with both trends and seasonality.

- **Decomposition:** Decomposition involves breaking down a time series dataset into trend, seasonal, and irregular components [90] [56], each representing underlying patterns in the data. The two main types of decomposition are additive and multiplicative. Additive decomposition is typically used if the seasonal variations are roughly constant over time, while multiplicative is used if the seasonal fluctuations change proportionally to the level of the trend.

2.1.3 Machine Learning and Modern Analytic Techniques in Demand Forecasting

Variance amplification is a common issue in multi-stage supply chains, where distortion of demand information gets amplified as it passes through different stages. This often negatively impacts upstream suppliers by making their operations less efficient. Research suggests that machine learning and other modern analytic techniques could help manage the variance amplification effect [35]. However, many of these machine learning techniques also have their shortcomings. Hence, in recent times, researches have combined multiple models and methods to make hybrid demand forecasting models that offer better accuracy and efficiency [35].

Machine Learning

Machine learning has increasingly become pivotal in enhancing demand forecasting. By leveraging large datasets and identifying complex, non-linear patterns, machine learning algorithms offer significant improvements over traditional statistical approaches. These sophisticated models adapt and learn from new data, enabling businesses to forecast demand with higher accuracy and efficiency. This adaptability is particularly beneficial in dynamic market environments where consumer preferences, economic conditions, and other influential factors evolve rapidly. The application of machine learning in demand forecasting represents a transformative shift towards more data-driven, predictive analytics in supply chain management, opening new avenues for optimization and strategic planning. Aamer et al. [1] discusses the machine learning methods that have been utilized across different industries and sectors, and asserts the advantages of machine learning models such as accuracy and efficiency over traditional models. Machine learning models typically used for demand forecasting have been delineated below.

- **Regression:** Regression models are a popular statistical approach for demand forecasting across various industries. Regression models establish relationships between a dependent variable (the forecasted element) and one or more independent variables (predictors). Various forms of regression include "linear, multiple, weighted, symbolic (random), polynomial, nonparametric, and robust" [77]. Ingle et al. [46] categorizes regression models into multiple regression, poisson regression, lasso regression and support vector regression. All these models have their applicability depending on the dataset and complexity of the problem. Regression models are valued for their interpretability, but their accuracy depends heavily on the choice of relevant predictors and the correct specification of the model.

- **Decision Trees and Random Forests:** Decision trees are a non-parametric supervised learning technique used for classification and regression problems [19]. These models work by recursively partitioning the data feature space into different regions with the goal of maximizing homogeneity in the response variable within each region. To build a decision tree model, the training data features and corresponding demand data labels are used. At each step in building the tree, the tree construction algorithm evaluates splits along each feature dimension to pick the one that best separates high and low demand based on metrics like information gain or gini impurity. In classification, the algorithm partitions the data to maximize label purity in the child nodes while regression trees aim to minimize the variance around response variable mean. Decision trees offer simple yet robust demand predictions, and often serve as base learners within ensemble techniques like random forests or gradient boosting machines.

  A random forest is an ensemble learning method, consisting of multiple decision trees for supervised classification and regression tasks [87]. Random forest constructs an ensemble predictive model by training a large set of decision trees, each built randomly using different subsets of data and variables, and combining their outputs. To build each individual decision tree, a random subset of features is selected to split each node. This process introduces randomness into each decision tree and decorrelates them from each other. During prediction, the random forest aggregates the predictions from each decision tree to output the overall prediction. By averaging many noisy but approximately unbiased trees, the variance of the random forest is reduced over a single decision tree. The main parameters to tune in a random forest are the number of trees constructed and the maximum depth allowed for each decision tree. Constraining both these parameters is important to limit overfitting and improve generalization [87] [82].

- **Neural Network-based Models:** Neural network-based models are models that mimic the structure and function of the human brain [45] to recognize patterns and relationships in data via artificial neurons. In demand forecasting, neural networks can handle complex, non-linear interactions within large datasets, which is useful in capturing the nuances of market dynamics [21]. Neural network based models can be especially effective when traditional forecasting methods fail to capture all relevant variables or when the relationships between these variables are too complex or non-linear. Examples of these models that have been used for demand forecasting include multilayer perceptrons (MLP), recurrent neural networks (RNNs) [49] and long short-term memory networks (LSTMs) [91].

- **Gradient Boost-based Models:** Gradient boost-based Models are ensemble-based machine learning techniques widely used for demand forecasting. They work by building a series of decision trees sequentially, where each subsequent tree attempts to correct the errors made by the previous one. This process involves optimizing a loss function by adding weak learners using a gradient descent-like procedure. Typical gradient-boost based models include light gradient boosting machine (LightGBM), categorical boosting (CatBoost) and extreme gradient boosting (XGBoost) [94].

Performance Evaluation for Machine Learning Models

The ability to evaluate and interpret model performance is crucial for understanding and improving predictive accuracy. In this section, we will explore several key metrics that are typically used to quantify prediction errors.

1. Mean Absolute Error (MAE)

   The Mean absolute error (MAE) measures the average absolute magnitude of the errors in a set of predictions [85]. It is the average of the absolute difference between the predicted and actual values [85].

$$\mathrm{MAE} = \frac{1}{n}\sum_{i=1}^{n} |y_i - \hat{y}_i|$$

2. Mean Squared Error (MSE)

   The Mean squared error (MSE) is a measure of the average of the squares of the errors between the actual and the predicted [85].

$$\text{MSE} = \frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2$$

3. Root Mean Squared Error (RMSE)

   The Root mean squared error (RMSE) is the square root of the average of squared differences between prediction and actual observation [85].

$$\text{RMSE} = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}$$

4. Coefficient of Determination (R^2 score)

   The coefficient of determination, often referred to as R^2 score, is a statistical measure that indicates the percentage of variation in the response variable that is explained by the predictor variables in a regression model [42].

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{\sum_{i=1}^{n}(y_i - \bar{y})^2}$$

In these formulas, y_i are the actual values, $\hat{y}_i$ are the predicted values, $\bar{y}$ is the mean of the actual values, and n is the total number of data points.

Hybrid Models

Hybrid models have emerged as an important approach for forecasting across a variety of domains. Hybrid models combine multiple component models in parallel, in series, or in a parallel-series structure, with the goal of improving forecast accuracy by leveraging the strengths of different modeling techniques. Key benefits of hybrid models include more comprehensive pattern detection, reduced risk from model selection, and simplified model selection processes. Parallel hybrids, which independently run multiple models and combine their forecasts, are most common and allow leveraging multiple modeling techniques. Series hybrids utilize the output of one model as input to a second model, allowing the components to play different roles. Parallel-series hybrids offer increased flexibility but can be complex to effectively design and tune. Hybrid techniques have become highly prominent for time series forecasting, with the structure offering distinct tradeoffs and benefits [43]. Ingle et al. [46] shares an example of ARIMA models and neural networks combined in series to improve accuracy in forecasting of daily product sales. Apart from the highlighted benefits, hybrid models can be complex, computationally intensive and difficult to maintain.

2.2 Lead Time Forecasting

Lead time forecasting is a critical aspect of supply chain management that involves predicting the amount of time required for a product or material to be delivered from the moment an order is placed until it reaches its destination. Accurate lead time forecasting is essential for organisations to optimize their inventory levels, minimize stockouts, and improve customer satisfaction. By leveraging historical data, analyzing supplier performance, and considering various factors such as transportation, production, and processing times, companies can develop robust lead time forecasting models.

2.2.1 The Significance of Lead Time in the Biotechnology Industry

Accurate lead time forecasting is crucial in the biotechnology industry to ensure timely production and supply of medicines and treatments, because availability of the required medicine at the right time can save lives. However, predicting lead times is extremely challenging due to the complexity of biomanufacturing processes and substantial variability in data [13]. The COVID-19 pandemic has further highlighted the importance of responsive and resilient biopharmaceutical supply chains that can rapidly scale up production and distribution to meet urgent patient needs. Current challenges include dealing with uncertainty around demand surges, raw material availability, logistics disruptions, and coordination across global supply networks. Supplier lead times have become more variable and lead time forecasting could allow the biotech companies to predict and avoid stock outs caused by a supplier, ensuring better supplier management and mitigation. In addition, lead time performance can be used as an evaluation criteria when selecting or retaining suppliers. With better prediction, it is possible for the pharmaceutical companies to define different levels of stock of the goods and manage challenges with demand variability, making the procurement process leaner and more cost effective [13]. Improved lead time forecasting through artificial intelligence and advanced analytics can support more precise capacity planning, inventory optimization, and proactive risk management. This is vital for biotech companies to cost-effectively deliver innovative therapies to patients without harmful delays, especially for diseases with narrow treatment windows or fast progression rates.

2.2.2 Conventional Methods of Lead Time Forecasting

Conventional methods of lead time forecasting typically focuses on statistical and heuristic techniques. These techniques include historical and moving averages, seasonal indexes, exponential smoothing and heuristics. These methods are similar to the traditional methods of demand forecasting discussed in Section 2.1.2.

2.2.3 Advanced Analytics for Lead Time Forecasting

The use of predictive analytics have been prevalent for lead time prediction. Machine learning models like regression, support vector machines, or neural networks can be used in predicting lead times based on patterns in historical data. These models have been discussed in detail in Section 2.1.3

In addition, real-time monitoring can also serve as a method for lead time forecasting. Internet of Things (IoT) devices and real-time analytics can be used to monitor and predict lead times based on live data from suppliers or logistic providers. IoT devices, such as sensors and trackers, can be deployed throughout the supply chain to continuously collect data on various aspects like inventory levels, shipment locations, environmental conditions, and production processes. Tracking shipments, production stages, and inventory levels in real-time allows for a dynamic understanding of lead times. Delays, bottlenecks, and disruptions can be identified as they occur, enabling immediate and actionable insights [10] [17] [28].

2.2.4 Factors Impacting Lead Time Variability

Lead time variability, which is critical to the effectiveness of a supply chain, is influenced by several factors. It is important to understand these factors in order to effectively create mitigation strategies to optimize a supply chain, thereby improving customer satisfaction, reducing costs, and most importantly in the case of a biotech company, save lives. The key factors impacting lead time variability include:

- **Supplier Reliability**: The consistency and reliability of suppliers significantly impact lead time variability. Suppliers with inconsistent production schedules or quality issues can cause fluctuations in lead times. The bullwhip effect, a phenomenon whereby there is an amplified upstream demand variability due to supply side variability being more than customer sales, is particularly more pronounced during supplier disruptions due to natural disasters [32].

- **External Factors:** Unforeseen events such as natural disasters, strikes, may impact supplier lead times. For example, as described in Ovezmyradov et al. [65], the COVID-19 pandemic led to significant supply chain disruptions that ultimately affected lead time variability for many companies. Changes in regulations or compliance requirements, especially in international trade, can introduce uncertainty and variability in lead times. Political instability or economic fluctuations in a supplier's region can unpredictably affect lead times.

- **Logistic Challenges:** The efficiency and effectiveness of logistic networks could impact lead time. Sometimes, logistic such as customs delay and shipping disruptions may cause massive changes to lead time, increasing its variability.

- **Demand Uncertainty:** Due to competition, market factors, consumer behavior, there is uncertainty and possibility variability of demand. This affects demand planning which could impact the supplier's ability to deliver, especially for suppliers with constrained capacity or multiple clients.

2.2.5 Strategies to Mitigate Lead Time Variability

Fluctuations in lead times make it difficult to reliably plan and meet consumer demands. However, a number of strategies can be employed to reduce inconsistencies and absorb variability in lead time. Effective mitigation of lead time variability involves deploying preventive measures to standardize processes, level workloads, and enhance reliability. It also requires building resilience through buffers and flexibility to handle the inevitable uncertainties. This balanced approach across both proactive and reactive policies can greatly improve predictability. Some of the strategies include having a diversified supplier base and supplier relationship management, advanced data analytics, and keeping safety stock or buffer inventory, among others.

Diversified Supplier Base

Having diverse suppliers reduces the risk associated with depending on a single source. This diversification can protect against disruptions and inconsistencies from any one supplier. This can be achieved and maintained by:

- **Multi Sourcing:** Multi-sourcing is a strategic approach in supply chain management where a company sources a single item or similar items from multiple suppliers. This strategy helps to mitigate risks and improve supply chain resilience. It also gives companies leverage for negotiation which could aid in better prices. This also ensures suppliers strive to improve the quality of their service and products. This strategy, however, requires more manpower and tools on the company side to manage these suppliers. In order to ensure proper management of these suppliers, it is important to segment them to better understand them. Rezaei et al. in [73] and [72] suggest segmenting suppliers using two criteria: their capabilities, which could span from technical, product quality to financial factors and their willingness to improve performance or collaborate, or be in a long-term relationship. Momiwand et al. [59] and Segura et al. [76] suggest using strategic performance which could cover products and purchase volume and critical performance, which could cover commercial risk and delays. All these methods of classifying suppliers ensure that the company is able to manage all its sources in a proactive manner [67].

- **Supplier Relationship Management (SRM):** SRM involves developing closer, more collaborative relationships with key suppliers to create and capture value and reduce risks. It involves integration and alignment, communication and information sharing, and working with suppliers to identify areas of continuous improvement. This helps foster supply chain resilience because it ensures a company has a deeper understanding of the suppliers' operations and risk exposure [59] [2] [11].

- **Geographical Diversification:** Sourcing from suppliers in different geographic regions can help to mitigate risks associated with local disruptions, economic downturns and other unforeseen circumstances that impact lead time.

Advanced Analytics & Forecasting

Advanced analytics methods can aid supply planning. In particular, these can be incorporated in the following ways:

- **Predictive Analytics:** Advanced machine learning models can use a multitude of data sources to better predict potential disruptions and variability. We can factor these analytics to account for a safety lead time that mitigates risks.

- **Simulation:** Simulations can be run to help better understand potential variability which would be instrumental in proactively creating strategies to manage them.

Buffer Inventory

Buffer inventory, also known as safety stock, is an additional quantity of a product or material kept in the inventory to reduce stock out risks. It acts as a buffer against unforeseen variations in supply and demand. The main purpose of maintaining buffer inventory is to ensure a steady supply and protect against uncertainties in the supply chain. Safety stock is extensively discussed in Section 2.3.

Vendor-Managed Inventory (VMI)

As described in Govindan et al [39], "Vendor-Managed Inventory (VMI) represents the methodology through which the upstream stage of a supply chain (vendor) takes responsibility for managing the inventories at the downstream stage (customer) based on previously agreed limits." In a VMI arrangement, the supplier takes responsibility for maintaining appropriate inventory levels on behalf of the buyer. The buyer provides the supplier visibility into point-of-sales data, forecasts, and any major events that may impact demand. The supplier then determines optimal replenishment quantities and frequencies needed to keep the buyer's inventory within established minimum and maximum boundaries. Advantages include increased operational resilience, reduced lead time variability, inventory carrying costs, stock out costs and demand uncertainty [81]. Challenges in implementing this include data security, complexity and supplier dependence.

Contractual Agreements and Incentives

Contractual agreements and incentives play a crucial role in managing supplier relationships and ensuring consistent lead times in the supply chain. Two key components of these arrangements are service level agreements (SLAs) and incentives for on-time delivery. By implementing these strategies, companies can foster stronger partnerships with their suppliers, reduce lead time variability, and improve overall supply chain reliability. The importance of SLAs and incentives in managing lead time variability are further described as follows:

- **Service Level Agreements (SLAs):** SLAs establish clear, measurable criteria for service delivery, ensuring that both parties have a common understanding of requirements, responsibilities, and performance metrics. SLAs ensure suppliers commit to specific lead times and reliability standards. SLAs also serve as a means to evaluate supplier performance.

- **Incentives for On-Time Delivery:** Incentives for on-time delivery in supplier management can help reduce lead time variability, thus ensuring a reliable and consistent supply chain. Effective incentive strategies can include performance-based pricing, recognition and awards, early payment and volume incentives, among others. These incentives can also help foster better supplier relationships.

2.3 Dimensioning Safety Stock

Uncertainty factors such as demand, supply and external events which affects operations are some of the key issues in supply chain management [37]. There has been much research into how to better manage such uncertainty especially in this competitive economic landscape, and safety stocks have been deemed suitable to account for demand and supply variability and a good strategy to prevent stockouts [37]. In this economic climate, and due to the recent supply chain disruptions globally, companies have become less tolerant to risk which, buttresses the need for safety stocks [37].

Safety stock is inventory carried to reduce the risk of or prevent stock outs. Factors that affect the probability of stock out includes forecast accuracy or inaccuracy, lead time variability and demand fluctuations. Some operations managers use either gut feel or an arithmetic sum of probable future demand or historical demand to determine safety stock. This methodology is prone to errors and does not adequately cover all the factors that affect stock out [50]. It is important to note that safety stocks are not meant to eliminate all stockouts, just majority of them [50] [70]. Goncales et al [37] among other authors believe safety stocks to be one of the best strategies to mitigate the supply and demand risks and uncertainty.

2.3.1 Existing Approaches for Determining Safety Stock

Goncalves et al. [37] did extensive work to research existing strategies to determine safety stock and summarise work by supply chain management academics. The authors compiled modeling techniques that have been studied, classified them, discussed the limitations and drawbacks, and identified ways to bridge the gaps for future research. As summarised by [37], and indicated above, the key factors that affect safety stock include service level, lead time, demand volatility, supply planning, scarcity of components and holding costs.

To address some of these key actors, there are standard stochastic approaches that have been developed to determine and calculate safety stock based on normally distributed parameters. In [75], [50], [37], [53], these approaches have been delineated as seen below.

When the major source of variability is the demand, the standard safety stock formula is the multiplication of the safety factor, which is dependent on the service level, based on a normally distributed demand and the standard deviation of the demand during the lead time [75][50]:

$$\text{Safety Stock} = z \cdot \sqrt{LT} \cdot \sigma_D \tag{2.1}$$

where z is the z-score or safety factor dependent on a service level. The z-score is obtained via the inverse of the standard normal distribution. LT is the lead time, and σ_D is the standard deviation of demand during the period of the lead time. Equation 2.1 is typically used when there is a future forecast available over the period of lead time.

In cases where there is historical data and the historical demand has deviated from the historical forecast, then the forecast error is the required protection to determine safety stock. Equation 2.2 is the best match to this scenario [75].

$$\text{Safety Stock} = z \cdot \sqrt{LT} \cdot \sigma_F \tag{2.2}$$

where σ_F is the standard deviation of the forecast error for the demand during the period of the lead time [75]. The standard deviation of the error is calculated from the mean squared deviation of the forecast versus actual demand.

It is important to re-iterate that the Equations 2.1 and 2.2 do not account for lead time variability.

When the variability in lead time is the major concern, then the formula can be modified to mitigate for that [75]:

$$\text{Safety Stock} = z \cdot \sigma_{LT} . D_{avg} \tag{2.3}$$

where D_{avg} is the average demand during the lead time period and σ_{LT} is the standard deviation of the lead time.

In cases where there is both lead time and demand variability, which is typically the case at Amgen, and both factors are independent, Equation 2.4 is used [50]:

$$\text{Safety Stock} = z \cdot \sqrt{LT \cdot \sigma_{D_{avg}}^2 + D_{avg}^2 \cdot \sigma_{LT}^2} \tag{2.4}$$

where σ_{Davg} is the average standard deviation of demand, quantifying the variability in demand during the lead time. The expression $LT \cdot \sigma_{D_{avg}}^2$ accounts for the variance in demand over the lead time. The term $D_{avg}^2 \cdot \sigma_{LT}^2$ accounts for the variance in lead time, weighted by the square of average demand.

In the event that the variability of lead time and demand are statistically not independent of each other, the safety stock formula can be defined as [50]:

$$\text{Safety Stock} = \left(z \times \sqrt{LT} \times \sigma_D\right) + (z \times \sigma_{LT} \times D_{\text{avg}}) \tag{2.5}$$

Goncalves et al [37] reviewed 95 peer-reviewed published papers from 1977 to January 2020 and established that the safety stock determination problem has often been tackled using analytical and optimisation models (e.g. stochastic methods, linear programming), simulation models (e.g, Monte Carlo simulation), or hybrid models (i.e. simulation based optimization techniques). In their review, 88% of the papers reviewed alluded to the use of analytical methods, while 6% use simulation models, and the rest use hybrid models. In addition, 35% of the 95 papers reviewed had industrial and practical contexts across the pharmaceutical, automotive, retail and electronic industry sectors.

In their study, Goncalves et al. [37] found that 35% of the analyzed papers adopted an approach for determining safety stock that accounts for demand variability. These studies utilized a range of techniques, from optimization methods to Monte Carlo simulation, aiming to size safety stock based on criteria such as service level, holding and ordering costs, backorder and setup costs, as well as the probability of stockouts.

Another approach described in several papers is based on an assumption that safety stock is proportional to forecasting errors and serves as a buffer strategy against forecast inaccuracies [37]. Some of the papers utilised the variance of forecast errors during the lead time demand, utilising techniques such as exponential smoothing to set safety stocks. The safety stock in Equation 2.2 alludes to this assumption by using the standard deviation of the historical forecast errors to calculate safety stock. Some interesting techniques employed in some of these papers used regression and forecasting methods to forecast demand, utilising variables like price and other external factors, and then estimating the errors from the models to set safety stocks. These outputs were fed into optimisation and simulation models to optimise for costs, stock out and inventory constraints. A third approach considered the effect to component standardisation and product structure on dimensioning safety stock.

Many of these approaches above have relied upon normally distributed and steady demand. In cases where the demand is not normally distributed or is intermittent, stochastic models have been used to address some of these. Zhou et al. [96] propose the use of bootstrapping to determine the variance of the time period demand, and utilise that to calculate safety stock at target service levels. The application of bootstrapping used in this case did not perform better than parametric methods when applied to an aerospace industry data set.

A couple of challenges with the existing methods are discussed in [38]. Some of these include:

1. **Assumption of normally distributed demand:** Inventory management relies on accurate forecast for demand, and demand forecast is an important input into determining safety stock. However, most of these papers and approaches in the industry have typically considered stationary or normally distributed demand, which is not the reality of major supply chains, especially those with multi echelons and products. Goncalves et al. [37] allude to using artificial intelligence methods to bridge the gap and perform multivariate demand forecasting.

2. **Supplier Disruptions:** Lead time plays a critical role in the calculation of safety stock levels. The unpredictability of supplier performance, especially in light of recent disruptions due to the pandemic, underscores the importance of employing predictive and descriptive analytics for risk management. These analytical tools enhance the reliability of safety stock calculations, addressing variabilities that may not have been adequately captured in previous approaches.

3. **Data Reliability and Quality:** As with any data-driven solution, credibility of data is always important to ensure effectiveness of the solution involved. Forecast variance

in the case of safety stock relies on the actual and predicted values being accurate and complete, as this impacts the safety stock levels.

4. **Multi-product Evaluations:** Most of these research studies have been based on single product inventory systems, and may not capture the dynamics of a multi-product supply chain environment. It is important to understand the risk profiles among multiple products.

2.3.2 Service Level

In inventory management, the service level is used to measure performance of inventory policies and represents the probability of not stocking out during the lead time [95]. Service level selection and determination are important, as the service level is directly proportional to how much buffer inventory should be held. The higher the service level, the higher the safety stock to be held [70].

Designing with a higher service level will requires higher safety stock. Safety stock level must be high enough that the company minimise the risk of stock out and is able to accommodate supplier lead times, but not too high such that the company loses money due to high holding cost and tied up working capital.

The optimal service level differs for each product. In the case of this project, each raw material differs from one to another based on customer sensitivity regarding stock outs for each product [70]. In most industries, the ABC analysis is used to determine an adequate service level for groups of products. The ABC analysis is typically done based on the revenue impact of inventory or products. Each category of product is assigned its own service level. Radasanu et al. [70] has formulated a sample service level segmentation as shown in Table 2.1.

Category	Segment	Description	Recommended Service Level (SL)
A	top 20%	critical few	high e.g. 96-98%
B	next 20-30%	interclass	medium e.g. 91-95%
C	last 50-60%	trivial many	lower e.g. 85-90%

Table 2.1: ABC Service Level Segmentation [70]

Customers will prefer a 100% service level but that is not advisable from a company perspective. It is important to understand that the service levels indicate the service performance of inventory, and are not a direct indicator of the performance of the firm in servicing a customer on time [22]. Ramos et al. [71] show the relationship between service and inventory levels in Table 2.2.

<table>
<tr><td rowspan="2"></td><td rowspan="2"></td><td colspan="2">Inventory Level</td></tr>
<tr><td>High</td><td>Low</td></tr>
<tr><td rowspan="2">Service Level</td><td>High</td><td>A (greater than 85%)
Fulfill customer demand, Carrying significant inventory</td><td>B (70-85%)
Optimum level, Achieve service level with balance inventory</td></tr>
<tr><td>Low</td><td>C (70-85%)
Excess inventory and Carrying nonperforming inventory</td><td>D (less than 70%)
Shortage and Stock-out</td></tr>
</table>

Table 2.2: Service Level vs. Inventory Level [71]

Service Factor or z-score

The z-score represents how many standard deviations an element is from the mean. In the context of service levels in inventory management or logistics, the z-score is referred to as the service factor, and is used to determine the safety stock level based on a desired service level. The z-score associated with a particular service level can be found using the inverse of the cumulative distribution function (often denoted as Φ^{-1}) of the standard normal distribution.

To compute the z-score from a given service level:

1. Determine the service level. For instance, a 95% service level would be represented as 0.95.

2. Use the standard normal distribution function to determine the z-score that corresponds to the cumulative probability of the service level.

The formula is given by [6]:

$$z = \Phi^{-1}(\text{Service Level}) \tag{2.6}$$

where z is the z-score, Φ^{-1} is the inverse of the cumulative distribution function of the standard normal distribution, and service level is the desired service level (e.g., 0.95 for 95%). The relationship between z-score and service level is shown in the graph in Figure 2-2.

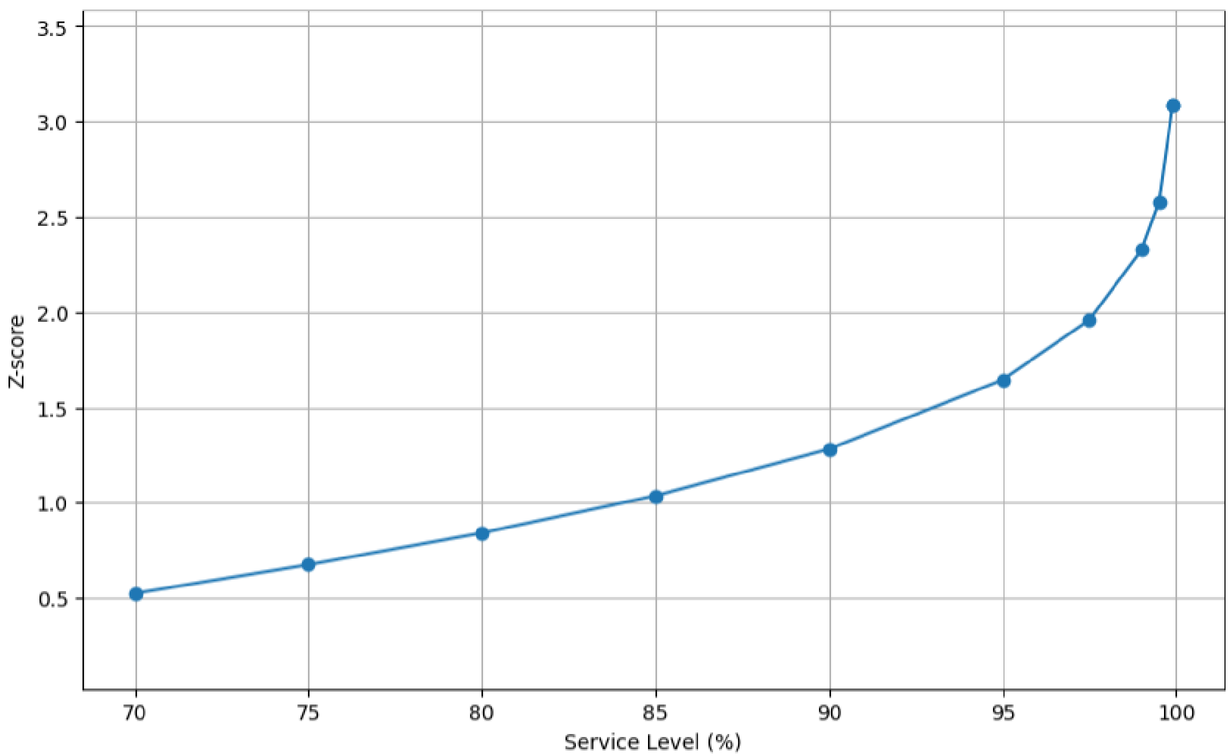

Figure 2-2: z-score for 70-100% Service Level

For a service level of 95% (or 0.95), z is approximately 1.645. This implies that for a 95% service level, the safety stock should be set at a level that covers 1.645 standard deviations above the mean demand during the lead time.

The service levels are used as a way to simulate risk tolerance for both inventory and the organisation. This is also proportional and related to the material or product segment and its importance and criticality to revenue generation and business value.

2.4 Integrated Inventory Management Methods in Literature

Several methods such as traditional forecasting, optimization, and inventory segmentation have been used by researchers and organisations over the years to manage and optimize inventory, and by extension the end-to-end supply chain. Methods utilized by researchers in the literature have been highlighted below.

Lolli et al. [54] proposes a multicriteria framework for inventory control and classification in manufacturing companies, particularly focusing on intermittent demand, and employs the analytical hierarchy process (AHP) to select the best alternative. Sinaga et al. [80] utilizes the traditional approach of simple moving average (SMA) for raw material forecasting using past consumption data and analytical hierarchy process (AHP) for supplier selection, based on criteria such as cost, quality and delivery time. The drive for the dual approach is to improve inventory management and supplier selection in organisations.

Brunaud et al. [18] aimed to reduce the forecast error in planning by using mixed-integer programming to determine the optimal flows and inventory policy parameters simultaneously. The researchers propose two inventory policies: the continuous-review (rQ) policy and the periodic-review (sS) policy, together with four safety stock formulations: "proportional to throughput, " "piecewise linear with risk-pooling," "explicit risk-pooling, " and "guaranteed service time" [18]. These models were used for simultaneous optimization of safety stock and base stock levels alongside material flows in supply chain planning [18]. They ran simulations on supply chain models and found that the piecewise linear and proportional formulations were less complex and yielded good results for single and multi echelon supply chains.

Most demand and inventory forecasts methods typically generate point forecasts and do not account for uncertainties around those forecasts in ensuring robust safety stock determination. Trapero et al. [86] proposes a novel approach based on combining empirical methods like the generalized autoregressive conditional heteroskedasticity (GARCH) and kernel density estimation (KDE) to model and forecast the demand distribution. Their result show that the optimal combination of these methods reduces the tick loss as it effectively captures the variability and asymmetry in demand distribution, leading to more robust safety stock forecasts and lower costs. Their research is an effort to explore further avenues to optimally estimate safety stock based on the logic that safety stock has a dependency on forecast error and its uncertainty.

Carbonneau et al. [20] explored the use of machine learning models like recurrent neural networks (RNN) and support vector machines (SVM) in comparison with traditional methods like moving averages and trends for supply chain demand forecasting. They run experiments on a canadian foundries sales data and found that the RNN and SVM models outperformed the traditional methods of forecasting by having better forecasting accuracy.Aamer et al. Aamer et al. [1] also reviewed 77 papers and highlighted that machine learning algorithms like SVMs, artifical neural networks(ANN), decision trees, random forest, and XGBoost have been used by researchers over the years for supply chain demand forecasting, with algorithms like XGBoost common in the healthcare sector.

Using simulation, Warren et al. [92] conducted a study on a three-echelon supply chain to assess how different combinations of forecasting methods, inventory policies, and lead times affect the total inventory costs. They explore the ant colony optimization (ACOR) algorithm, a metaheuristic technique, for demand forecasting and inventory optimization. However, they identify future exploration of the impact of lead time variability and improved communication on the supply chain. Wadhwa et al. [89] also used simulation to investigate the performance of various inventory policies in a four-echelon supply chain. They model the supply chain as a network of autonomous nodes and simulate these policies under conditions of sudden demand changes. They discover that independent decision making at each node leads to the bullwhip effect, distorting demand information in the supply chain. They also assert that machine learning plays a vital role in transparent collaborative supply chain planning. Mansur et al. [55] also used Monte Carlo simulation to model inventory cost minimization and optimization of blood inventory platelet levels.

Fabianova et al. [34] explores the use of quantitative forecasting with methods such as autoregressive integrated moving average (ARIMA) and Monte Carlo simulations with optimization for production planning. They implemented these methods on data from a company producing and selling paper hygenic products. Their study showed that these methods were effective in production planning and reducing cost. They also identify that the simulation was beneficial for risk analysis and was most effective when the input variability was low.

Zwaida et al. [4] explores the use of deep reinforcement learning (DRL) to automatically make a drug refilling decision in order to prevent stock outs. The researchers use a Markov decision process model and a deep Q-learning framework to address the drug shortage problem and minimize cost in hospital supply chains. Plessis et al. [30] also used reinforcement learning (RL) to investigate inventory management improvement in pharmaceutical supply chains. These researchers make use of an agent-based simulation model to evaluate the effectiveness of various information sharing scenarios in order to mitigate supply chain inefficiencies.

Goncalves et al. [37] made an effort to consolidate and review research on methods of dimensioning safety stock and highlight gaps and areas for future work. They review 95 academic papers published between 1977 and 2019. They reviewed papers that explored the variation of normally distributed demands, forecasting errors, component standardization, stochastic models, simulation-based optimization models and mathematical programming models to dimension safety stock. Their study identifies a significant gap in current research regarding the impact of supply chain disruptions on safety stock and inventory management.

In summary, researchers have explored a variety of quantitative techniques for optimizing inventory management and safety stock determination, including traditional forecasting, machine learning, simulation, and optimization methods. However, several gaps exist regarding the integration of predictive analytics to account for demand uncertainty and supply variability, especially amidst disruptions. There is also a need for more practical implementations that address the constraints of complex multi-product supply chains through custom segmentation and policy development. As reinforced by the COVID-19 pandemic, building supply chain resilience requires a balanced approach using advanced analytics while also exploring organisational and operational methods to mitigate risk. This review highlights critical opportunities to integrate data-driven insights with simulation of uncertainties and organizational alignment. The path forward necessitates cross-functional collaboration and change management to unlock the full potential of inventory optimization and management.

2.5 Limitations of Data-Driven Approaches

Despite the numerous benefits such as improved accuracy and inventory optimization associated with implementation of data driven approaches for inventory management, there are some limitations and challenges to using data as opposed to the traditional approaches. Some of these limitations are delineated below.

Data Quality, Security and Integration Challenges

- **Data Quality and Accuracy:** Ensuring data accuracy is paramount. Inaccurate data can lead to erroneous forecasts and sub-optimal inventory decisions.
- **Integration of Diverse Data Sources:** Consolidating data from multiple sources (internal systems and teams, suppliers, market trends) is complex. It requires harmonizing different data formats and ensuring consistent data quality across sources.
- **Legacy Systems Integration:** Older enterprise systems pose challenges for data connectivity needed for optimization and analytics systems.
- **Data Security and Privacy:** Protecting sensitive supply chain data, especially in collaborations with third parties, is essential to prevent data breaches.

Technical and Infrastructure Challenges

- **Real-Time Data Processing:** The need for real-time analytics demands robust IT infrastructure capable of handling large data volumes easily. This requires expert personnel and can be costly.
- **Cost and Complexity of Implementation:** Setting up advanced data analytics systems involves significant costs, including investments in technology and human resources.
- **Scalability:** Systems should be scalable to accommodate growing data volumes and evolving business requirements.

Organizational and Human Resource Challenges

- **Change Management:** Implementing new data-driven approaches can meet resistance from employees accustomed to traditional methods. This necessitates organizational changes, including training staff, adapting business processes and behavioral ways of thinking.

- **Analytics and Business Expertise:** A shortage of skilled personnel who can both interpret complex data and derive actionable insights can be a critical bottleneck.

Modeling and Predictive Analysis Challenges

- **Predictive Model Selection and Accuracy:** Selecting the most appropriate model for the data context and needs can be complex, and choosing the wrong one can lead to inaccurate predictions. Developing and maintaining accurate predictive models is challenging, especially in dynamic market conditions.

- **Computational Complexity:** Inventory systems with thousands of SKUs, complex constraints, probability distributions etc. become complex to manage due to large number of variables.

- **Maintenance of Models:** Real-time data feeds, frequent retraining of models, updating business rules, market conditions, etc., are essential but requires manpower. Lack of adequate maintenance impacts robustness and accuracy of models.

- **Interpretability and Explainability:** Data-driven models can be complex and opaque, making it difficult to understand why certain decisions are made. Ensuring transparency and explainability is crucial for building trust and managing risk. Not all predictive models are easily explainable and this needs to be factored into decision making when choosing models if it is a priority for the organisation.

- **Accounting for external factors:** Forecasts can be heavily affected by external factors like sales promotions, economic fluctuations, and weather, which can be difficult to model and predict accurately.

Chapter 3

Methodology

The scope of this project is limited to raw materials required to produce the drug substance, drug products and finished drug product which are the higher stages of production in Amgen. The complexity of this project stems from the fact that the higher stages for drug production have substantial impact on the lower stages, and this fact informs the raw material planning strategy of the organisation which influences the safety stock determination. These nuances inform the approach that will be discussed in this chapter.

As discussed in Chapters 1 and 2, the key sources of variability and fluctuations are the demand and supplier lead times. The demand plan of the raw materials is, however, influenced by the finished drug product forecast by the organisation. This forecast is an internal factor, but is influenced by external factors such as market conditions, consumer behavior, etc., and the supplier lead times, which is hard to control, but which the company can influence.

In Chapter 2, approaches researched have been summarised with gaps such as data, supplier disruption, and demand distributions identified to further enhance the safety stock determination methodologies.

3.1 Project Context

The context and challenges of this project are as follows:

- **Scope:** The scope of the project is limited to raw materials; however, the implemented methodology is quite applicable to upper echelons in the supply chain at Amgen. This brings a different level of complexity as the demand forecast is currently done at the top of the supply chain, which is the finished drug product (FDP) level. The raw material plan is drawn from the FDP forecast for those on bill of materials (BOMs) and using historical data for miscellaneous materials such as gloves, secondary packaging, etc., that are classified as non-BOM at Amgen.

- **Frequency of Forecast Update:** Due to the forecast being run at the FDP stage of production, the forecast gets updated daily, with the monthly cycle captured at the end of each month. This means that the raw material plan changes and is variable depending on the FDP forecast and signal from the market. Due to the lead time constraint for raw materials, if a forecast changes during the period of the lead time of the raw material, there are limited mitigation or response actions that can be taken to accommodate the increase or decrease in raw material requirement. These variations definitely affect the safety stock levels.

- **Volume of Raw Materials:** This is a multi-product supply chain and the scope of work covers over 10,000+ raw materials used to produce over 20 finished drug products. It is also important to note that this is a growing supply chain with the final drug products at different lifecycle stages and different revenue generation.

- **Lead Time Challenges:** The agreed lead times at the time of the project were being used as target lead times by the team for supply planning and thus are not significant in calculating safety stock. Some of the suppliers do not have an exceptional track record of keeping to agreed lead times. This ultimately shows a gap in the raw material planning currently being done in the organisation.

- **Segmentation:** An ABC inventory type segmentation was developed and implemented for the finished drug products to determine the safety stock policy in the form of months forward coverage (MFC) policy. However, for raw materials, there is not a formalized ABC segmentation process and the safety stock policy is site specific and is currently being set by the different manufacturing plants. It is important to note that there are similar raw materials being used across multiple sites and there is room for network sharing.

- **Data storage:** There are currently some data gaps in the historical data. These are being fixed and a sustainable pipeline is being built to properly store historical data. The organisation is starting to build and maintain data pipelines to ensure that data-driven implemented solutions are sustainable in the long run.

3.2 Proposed Methodology for Safety Stock Calculation

The approach is to estimate safety stock as a decision variable, leveraging the formulas and methodology from the literature, as discussed in Chapter 2. The key inputs into the safety stock formulas are the lead time and demand models, which are treated as prediction variables. Machine learning models are built to predict the lead time and the demand, while addressing the identified challenges and sources of inventory risk and variability. The outputs of the models feed into the safety stock formula. Amgen currently has a 95% service level policy which also feed as the baseline to the formula, with a variation of 90% - 100% service levels to show the difference in inventory levels at those service levels and guide management decisions. Monte Carlo simulation is also performed on the safety stock, varying the lead time and demand to show the impact on safety stock and stock levels if the lead times and demand deviate from target. It is important to note that this work is applied on thousands of materials, hence, most of the models built are cluster based to ensure sustainability in the long run. The proposed methodology is illustrated in Figure 3-1.

The proposed methodology presents a unique contribution to the field of inventory management. While existing approaches often rely on static assumptions and simplified models, this methodology integrates machine learning-based demand and lead time forecasting with stochastic simulation and multi-criteria segmentation. This holistic approach allows for a more accurate and dynamic determination of safety stock levels, considering the complex interactions and uncertainties in the supply chain. By incorporating real-time data and adapting to changing conditions, our methodology offers a significant advancement over traditional inventory management techniques.

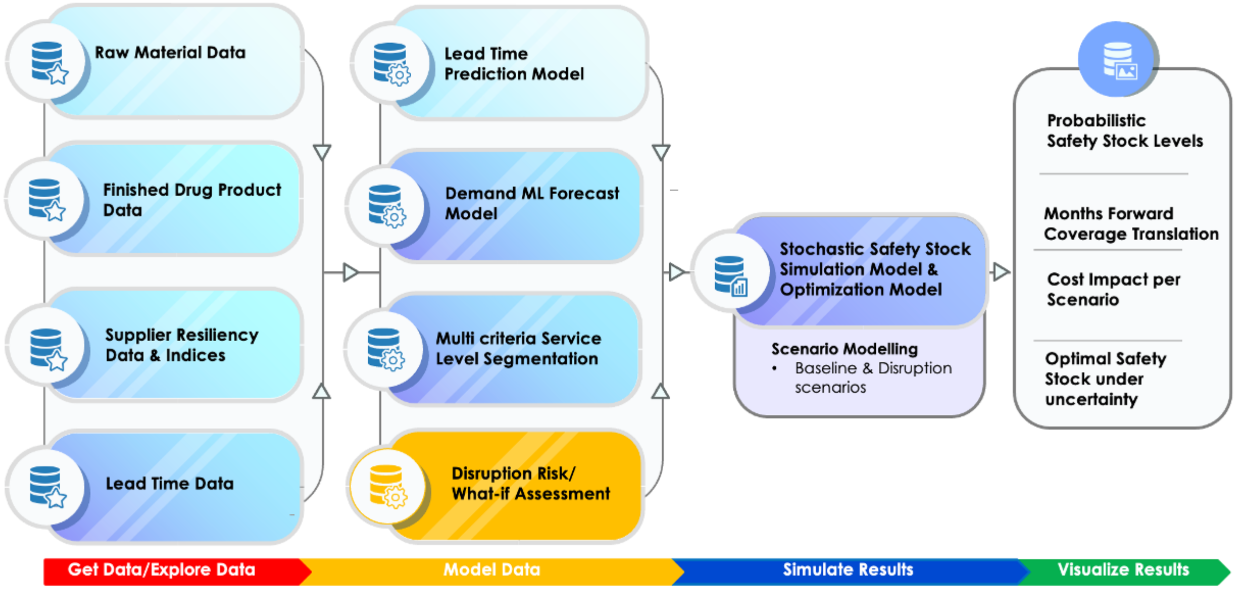

Figure 3-1: Proposed Methodology for Safety Stock Determination

3.2.1 Baseline Methodology

The following steps delineate the procedures followed to determine the optimal safety stock accounting for demand variability, lead time and what-if scenarios.

- **Step 1:** Lead time and lead time variance forecasting
- **Step 2:** Demand forecasting or demand forecast accuracy normalisation on demand Plan
- **Step 3:** Service level determination via segmentation
- **Step 4:** Fit the distribution of demand from step 2 using lead time from step 1
- **Step 5:** Utilise steps 1 - 4 as input into a Monte Carlo simulation to generate numbers based on distribution fitting and into the safety stock formula

3.2.2 Step 1: Supplier Lead Time and Lead Time Variance Forecasting

The supplier lead time is the time elapsed between when the order is placed and when the supplier or vendor delivers the items to the plant or warehouse. Since Amgen has limited influence on a supplier delivery time, and is not privy to all the other clients or schedule. or constraints of a supplier, it is important to be able to forecast the supplier lead time leveraging historical performance.

In the biotech and healthcare sector, timely delivery of services and products are crucial to saving patients' lives. The supply chain lead times are directly proportional to the availability of medicines in healthcare institutions [13]. Being able to ensure that Amgen is able to meet "Every patient, Every time," the company needs to anticipate the behavior of external parties, specifically in this case, the suppliers. Accurate and credible forecasting of the lead time of raw material supply can assist in optimising production processes, reduce production schedule changes caused by unavailability and allow for an optimal safety stock level decision.

A couple of techniques have been historically used to determine and predict lead times. Some companies have simply used the average of actual lead times to determine future performance. With the advent of artificial intelligence, better data infrastructure available, less conventional methods have been utilised to predict lead times. These methods have been delineated in Chapter 2. The organisation has a data science team. However, since Amgen is not a data science organisation, it is important to demonstrate the business case, and for the key executives to understand the factors driving the models. Therefore, key factors that have gone into consideration for the method selection include the data availability, maintainability and sustainability, and model explainability and interpretability. As a result, regression, gradient boosting and decision tree models have been utilized for forecasting the lead time. More details will be discussed in the following sections.

Dataset, Data Sources and Data Preprocessing

The major data sources for the forecasting models are the historical purchase orders for orders placed from January 2016 to June 2023, and the supplier resiliency index data for about 10,000 raw materials. These datasets are stored in the company's enterprise data lake and were queried using structured query language (SQL). Both datasets were combined and merged on the material ID to give a combined dataset with 78,913 rows. The combined dataset contained the following columns as described in Table 3.1.

Field Name	Description	Data Type
purchasing_doc	Purchase order ID	String
material description	Description of the material	String
material	Raw Material ID	String
plant	Manufacturing Plant ID	String
material category	Category of the material	String
material_sub_group	Sub group of the material category	String
Vendor ID	The supplier ID	String
Vendor Name	The name of the supplier/vendor	String
po_quantity	The quantity of the items in the purchase order	Float
order_plcmt_dt	Date the order was placed	Date
pl_deliv_time	The planned/agreed delivery time of the order	Integer (days)
GR_Date	The goods receipt date of the raw material	Date
Invoice_Value	The value of the invoice or PO	Decimal
actual_LT	The actual lead time	Integer (days)
placed_days_in_advance	Number of days the order was placed early or late	Integer
material_sourcing_complexity	The company's ranking of the sourcing complexity	Float (Rating)
multi_sourcing	The company's ranking of if there are multiple sources	Float (Rating)
supplier_relationship	The company's ranking of how the supplier is easily managed or influenced	Float (Rating)
primary_source	If the vendor is the primary source (Yes/No)	Boolean
Country Match	Manufacturer and plant in the same country (1/0)	Boolean
Region Match	Manufacturer and plant in the same region (1/0)	Boolean

Table 3.1: Descriptive Table of Data Fields for Lead Time Forecasting

Data Preprocessing

The following preprocessing steps were performed on the data:

1. The materials were categorised into bill of materials (BOM) and non-bill of materials (Non-BOM); *yes* for BOM, *no* for non-BOM. Refer to Table 1.1 for categorisation.

2. All columns were converted to their appropriate data types.

3. There were some observed anomalies in data in which some of the actual lead times were negative; so those data points were filtered out.

4. Duplicate entries on the purchasing order ID and order_plcmt_dt columns were removed.

The preprocess_data function below was also created to ensure that all the required features in the model were properly preprocessed and encoded where appropriate before the model was trained.

Algorithm 1 preprocess_data

```
procedure PREPROCESS_DATA(group_data)
    α = Extract month from 'order_plcmt_dt' in group_data
    X = Select columns from group_data
    Create dummy variables from categorical columns in group_data, store in β, γ, δ, ϵ, ζ
    X = Concatenate X with β, γ, δ, ϵ, ζ
    y = Extract 'actual_LT' from group_data
    return X, y
end procedure
```

α Extracted month from 'order_plcmt_dt' in group_data.

β Dummy variables created from the 'order_unit' column in group_data.

γ Dummy variables created from the 'MATERIAL CATEGORY' column in group_data.

δ Dummy variables created from the 'PRIMARY_SOURCE' column in group_data.

ϵ Dummy variables created from the 'COUNTRY_MATCH' column in group_data.

ζ Dummy variables created from the 'REGION_MATCH' column in group_data.

The input features used in training X are 'po_quantity', 'pl_deliv_time', 'placed_days_in_advance', 'Material Sourcing Complexity', 'Multi-sourcing', 'Supplier Relationship', 'Month', 'order_unit', 'material_category', 'country_match', and 'region_match'. The target variable y is the 'actual_LT' column.

Model Selection

Explainability was a priority in model selection; therefore, the following models are considered: light GBM regressor, XGB regressor, random forest regressor, linear regression and lasso regression. The dataset for training contained a total of 78,913 points with 46,027 points for the non-BOM cluster and 32,886 points for the BOM cluster. Algorithm 2 is used to select these models. In this algorithm, α are the hyperparameters of the selected model type. Details of the hyperparameters can be found in Table A.1 in the appendix.

Algorithm 2 get_model_params

!h

```
procedure GET_MODEL_PARAMS(model_type)
    if model_type equals 'lgb' then
        α = LGBMRegressor hyperparameters
    else if model_type equals 'xgb' then
        α = XGBRegressor hyperparameters
    else if model_type equals 'rf' then
        α = RandomForestRegressor hyperparameters
    else if model_type equals 'linear' then
        α = LinearRegression hyperparameters
    else if model_type equals 'lasso' then
        α = Lasso hyperparameters
    end if
    return α
end procedure
```

Training and Testing

The following approach is used to train and test the models. A 70/30 time series split is used to demarcate the training and testing dataset. The hyperparameter tuning for each model is based on the hyperparameters as defined for each model in Table A.1. The model training is cluster based; models are built for BOM materials separately from non BOM materials.

The evaluate_group function is used to evaluate the training and test data performance as shown in Algorithm 3. In this algorithm, $[\alpha]$ are the hyperparameters of the selected model type obtained from the get_model_params function, $[\beta]$ are the predicted values for the training set y_{train} obtained using the best_model, and $[\gamma]$ are the predicted values for the test set y_{test} obtained using the best_model.

Performance Evaluation

The MAE, MSE, RMSE and R^2 score are used to evaluate the model performance for

Algorithm 3 evaluate_group

procedure EVALUATE_GROUP(BOM, group_data, model_type)
  (X, y) = Call preprocess_data with group_data
  Split X and y into training and testing sets, store in X_{train}, X_{test}, y_{train}, y_{test}
  α = Call get_model_params with model_type
  Initialize model with α
  Initialize GridSearchCV with model and α, store in grid_search
  Fit grid_search with X_{train} and y_{train}
  best_model = Best model from grid_search
  β = Predict y_{train} values using best_model
  $r2_{\text{train}}$ = Calculate R-squared score of y_{train} and β
  γ = Predict y_{test} values using best_model
  mae = Calculate mean absolute error of y_{test} and γ
  mse = Calculate mean squared error of y_{test} and γ
  $rmse$ = Calculate root mean squared error from mse
  $r2_{\text{test}}$ = Calculate R-squared score of y_{test} and γ
  return mae, mse, $rmse$, $r2_{\text{train}}$, $r2_{\text{test}}$, best_model, X_{train}, y_{train}
end procedure

the five models used in training. The principle and formulas for these evaluation metrics have been described in Chapter 2. After training and testing, a summary of the performance evaluation results are shown in Table 3.2.

Model	**BOM**	**MAE**	**MSE**	**RMSE**	R^2 **train**	R^2 **test**
Results for the Non-BOM Cluster						
XGBoost	no	5.84	292.09	17.09	0.87	0.81
Random Forest	no	6.98	270.12	16.44	0.97	0.82
Light GBM	no	6.03	300.87	17.35	0.83	0.80
CatBoost	no	5.68	241.80	15.55	0.87	0.84
Results for the BOM Cluster						
XGBoost	yes	38.40	5138.22	71.68	0.90	0.76
Random Forest	yes	54.02	7457.08	86.35	0.98	0.65
Light GBM	yes	38.78	4997.41	70.69	0.88	0.76
CatBoost	yes	37.54	4887.67	69.91	0.88	0.77

Table 3.2: Model Performance Comparison on Test Data for Lead Time Prediction

Comparing all the models with the R^2 performance metric, as shown in Figure 3-2, the CatBoost models have the best performance for both clusters. The XGBoost and LightGBM come very close to performing as well as CatBoost. CatBoost also has better performance when comparing other metrics in Table 3.2

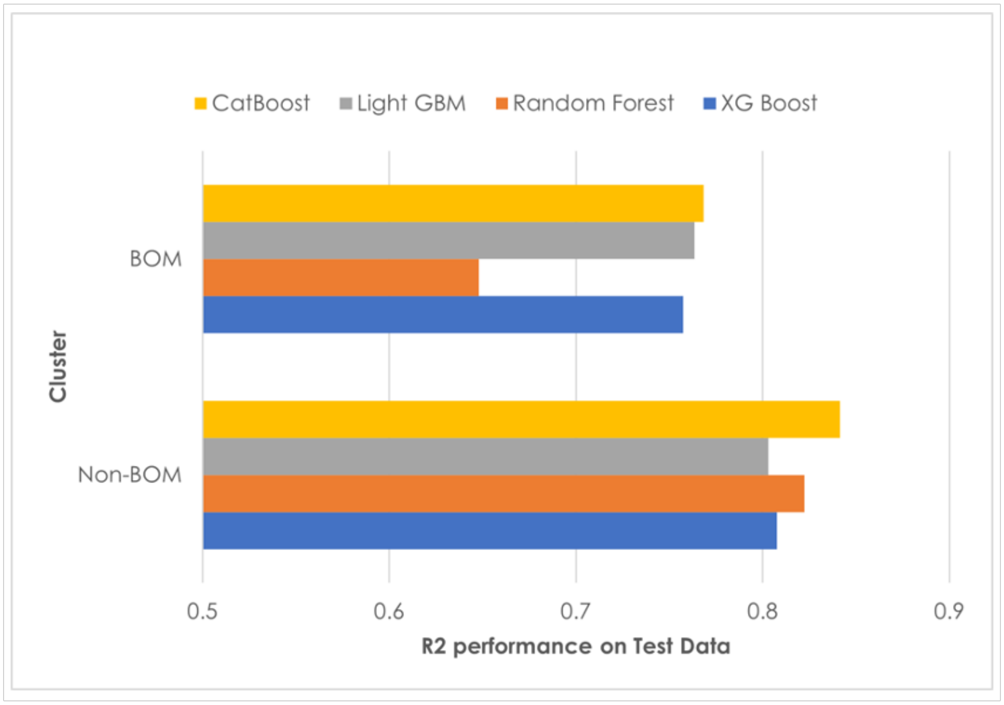

Figure 3-2: Model Performance Comparison for BOM and Non-BOM

Feature Importance

The feature importance is generated based on the output of the trained models. The feature importance of the highest performing model, CatBoost is shown in Figures 3-3 and 3-4. We see that the planned or agreed lead time has the highest importance, as expected.

In both clusters, the planned lead time is an important feature. However, more importantly, we also see that whether an order is placed on time, early, or late (designated by the placed_days_in_advance feature) has a significant impact on the performance of the model.

Lead Time and Variance Prediction

The model predicts the expected actual lead times for the raw material. However, the safety stock formula still requires the variance of the lead time. Due to the fact that the planned lead time at the time of order placement has historically changed and the actual lead times are compared to the planned, performing a mathematical calculation of the historical variance will build in bias into the model, because it does not account for the target lead

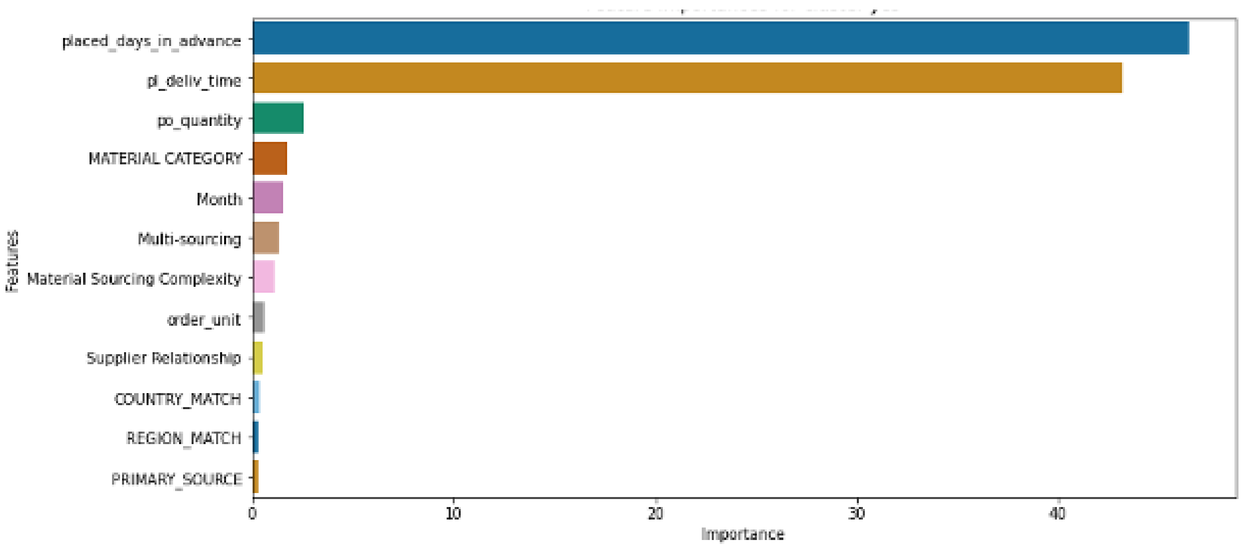

Figure 3-3: CatBoost Model Performance for Non-BOM Cluster

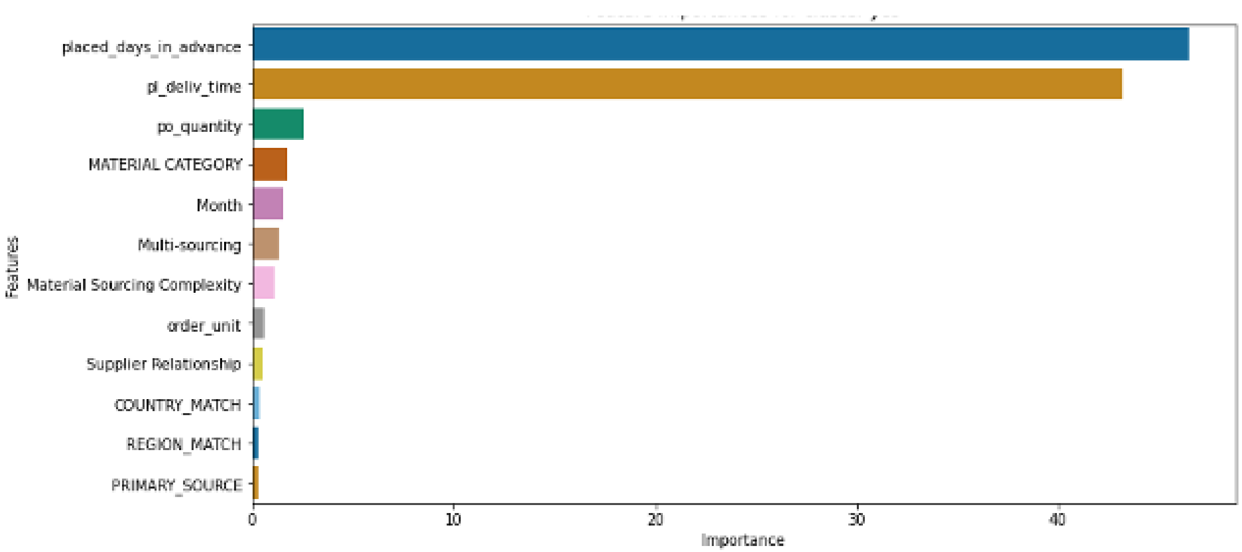

Figure 3-4: CatBoost Model Performance for BOM Cluster

time at the time of order placement. Therefore, since all these data points are part of the training sample for the model, the likely variance of the prediction based on this historical performance can be estimated using bootstrap aggregation or model residuals.

Data Preparation for New Prediction

To run the new predictions using the trained models, the data needs to be thoroughly processed and passed through the prediction functions in the same format and type as the data used in model training. Therefore, Algorithm 4 is implemented to ensure proper preprocessing of new data. In this algorithm, α] represents the data after converting specific columns ('pl_deliv_time', 'placed_days_in_advance', 'Material Sourcing Complexity', 'Multi-sourcing', 'Supplier Relationship') to numerical values. [X] indicates the selected necessary columns from α.

The dummy variables β are created from the 'order_unit' column in α.

The dummy variables γ are created from the 'MATERIAL CATEGORY' column in α.

The dummy variables δ are created from the 'PRIMARY_SOURCE' column in α.

The dummy variables ϵ are created from the 'COUNTRY_MATCH' column in α.

The dummy variables ζ are created from the 'REGION_MATCH' column in α.

Algorithm 4 preprocess_data

```
procedure PREPROCESS_DATA(data)
    Convert columns in data to numeric values, store in α
    X = Select necessary columns from α
    Create dummy variables from categorical columns in α, store in β, γ, δ, ϵ, ζ
    X = Concatenate X with β, γ, δ, ϵ, ζ
    Scale numerical features in X if necessary
    return X
end procedure
```

Model Residuals Based Prediction

A way to enhance prediction accuracy is utilization of residuals from a previously trained model. A residual is the difference between the observed value and the value predicted by the trained model [85]. Residuals help reveal patterns that the model has not captured. The prediction intervals are calculated using the percentiles of the residuals. Prediction intervals provide a range within which future observations are expected to fall with a certain probability, taking into account the variability that the model has shown on the training data. The residual_prediction function implemented in Algorithm 5 implemented below is adjusts new predictions based on the residuals of the model, and then calculates the prediction intervals to derive the the lead time variance [84].

Bootstrap Aggregation(Bagging)

Bootstrapping is a method of generating prediction intervals for stochastic independent variables which does not assume normal forecast errors, and explicitly incorporates the

Algorithm 5 residual_prediction

procedure RESIDUAL_PREDICTION(row, results_df)
  $X_{\text{new}} \leftarrow$ Call preprocess_data with row
  $\alpha \leftarrow$ Extract 'BOM' from row
  $\beta, X_\alpha, y_\alpha \leftarrow$ Extract 'model', 'X_train', 'y_train' from results_df corresponding to α
  for column in X_α columns **do**
    if column not in X_{new} columns **then**
      Add column to X_{new} and fill with zeros
    end if
  end for
  Update X_{new} to only include columns present in X_α
  Fit β with X_α and y_α
  $y_{\text{predicted\_alpha}} \leftarrow$ Predict using β on X_α
  $\gamma \leftarrow y_\alpha - y_{\text{predicted\_alpha}}$
  $y_{\text{pred}} \leftarrow$ Predict using β on X_{new}
  Calculate prediction intervals using γ percentiles
  $\delta \leftarrow$ Calculate standard deviation of γ
  return Series with row details, y_{pred}, γ, mean of y_{pred}, prediction intervals, and δ
end procedure

additional uncertainty due to estimation of exogenous variables [57]. Boostrapping can help improve the forecast accuracy of machine learning models relative to traditional methods [23]. The technique helps to reduce variance without increasing bias of the predictions and therefore results in more accurate point predictions [68]. Bootstrapping is a versatile and practical technique that does not make rigid assumptions about data distribution and is applicable to various types of data and machine learning models. However, it can be computationally intensive to implement, especially with large datasets and complex models. It also may not work well if the sample size is too small, and assumes that the sample is a representative of the population, which is not always true. A way to combat the sampling challenge is to run many iterations.

To make new predictions, the bootstrap prediction technique is used to generate an ensemble of predictions for a new observation, each made by a model trained on a different resample of the training data. The distribution of these predictions is then used to estimate the uncertainty of the prediction for the new observation.

Algorithm 6 implements the bootstrap aggregation methodology to generate future predictions.

Algorithm 6 bootstrap_prediction

procedure BOOTSTRAP_PREDICTION(row, results_df, n_iterations)
  X_{new} = Call preprocess_data with row
  α = Extract 'BOM' from row
  $\beta, X_{\text{train}}, y_{\text{train}}$ = Extract 'model', 'X_train', 'y_train' from results_df corresponding to α
  Update X_{new} to include any missing columns present in X_{train}, fill with zeros
  Update X_{new} to only include columns present in X_{train}
  Initialize an empty list, γ
  for i in range(n_iterations) **do**
    $(X_{\text{resample}}, y_{\text{resample}})$ = Resample X_{train} and y_{train}
    Fit β with X_{resample} and y_{resample}
    y_{pred} = Predict values using β and X_{new}
    Add y_{pred} to γ
  end for
  γ = Convert γ to array
  δ = Calculate percentile of γ
  ζ = Calculate standard deviation of γ
  return Series with row details, predictions, mean prediction, prediction interval, and prediction standard deviation
end procedure

Here,

α is the identifier 'BOM' extracted from the input data row, used to select the corresponding model and training data from the results dataframe (`results_df`),

β represents the predictive model (`best_model`) retrieved from the results dataframe (`results_df`), which corresponds to the 'BOM' identifier found in the input data row,

γ is a list of predicted outcomes (`predictions_list`) generated from multiple bootstrapping iterations, using the model (`best_model`) and the processed input data row,

δ represents the prediction interval, calculated based on the percentile of the bootstrapped predictions list (γ or `predictions_list`),

ζ indicates the standard deviation of the predictions list (γ or `predictions_list`), measuring the variability of the bootstrapped predictions.

X_{new} refers to the processed features obtained from the input data row, formatted to match the model's (`best_model`) input requirements, and finally,

X_{train}, y_{train} denote the training dataset extracted from the results dataframe (`results_df`), which is associated with the 'BOM' identifier from the input data row and used for model retraining and prediction.

It is recommended that bootstrap aggregation be used if there is enough processing power and storage to run the predictions. However, because the lead time forecasting is cluster based with different materials in a cluster, a more advanced technique like bootstrapping is preferred in order to predict the variance, because the assumption that the residuals are homoscedastic and normally distributed, meaning that they have the same variance for all predicted values, does not hold for this use case. Also, since the lead time predictions only need to be run periodically, the additional computational cost for boostrapping is marginal.

3.2.3 Step 2: Demand Forecasting for Raw Materials

The importance of and methods for demand forecasting have been described in detail in Section 2.1. In order to manage stock inventory to limit losses, organisations have historically utilised time series forecasting, machine learning algorithms and optimization to predict demand. The longer the lead time, the lower the forecast accuracy. Therefore, to mitigate the effects of long lead times, it is important to minimize demand forecast inaccuracy [35]. For the use case of the raw materials, the following models have been selected: light gradient boosting machine (LightGBM), extreme gradient boosting (XGBoost), Random Forest and categorical boosting (CatBoost). These models have been selected because they can handle large datasets, they can capture complex relationships between features and the target variable, they are robust to overfitting and they have shown high predictive accuracy in use cases in the literature. Random forest and the boosting algorithms (XGBoost, LightGBM, CatBoost) use ensemble learning, which combines multiple models to improve predictions and reduce variance. CatBoost in particular is able to handle categorical data without encoding. Also, it is easier to explain, interpret and understand the feature importance of these models than in neural network-based models. In structured data prediction type problems, decision tree-based algorithms are also more efficient than neural network-based algorithms [60].

Data Preprocessing

Dataset

The major data sources for the forecasting models are the historical demand plan and material details from an internal Amgen database managed by Kinaxis Rapid Response [47], and actual consumption from systems applications and products in data processing (SAP) with duration August 2019 to June 2023. These datasets are stored in the company's enterprise data lake and were queried using SQL. All datasets were combined and merged on the material and plant ID to give a combined dataset with 384,911 data points or rows of data. The combined dataset contained the following columns as shown in Table 3.3.

Feature Name	**Description**	**Type**
total_demand	Demand plan from the FDP forecast bill of materials	Integer
material	ID of the material	String
material description	Description of the material	String
plant	Manufacturing Plant in which the material is utilized	String
material category	Material category	String
material_sub_group	Sub group of the material in the category	String
year_month	Date when the forecast value is required	Date
month	Month when the forecast value is required	Integer
months_offset	How many months in advance the forecast was made	Integer
uom	Unit of measurement in which the demand plan of the raw material is made	String
hist_consumption	Actual consumption for each year_month (target variable)	Integer

Table 3.3: Description of Dataset Features for Demand Forecasting

Data Preprocessing

The following preprocessing steps were performed on the data:

1. The materials were filtered to only contain BOM materials and clustered using their material category.
2. All of the columns were converted to their appropriate data types.

3. Null values were removed.

Algorithm 7 implements a function created to ensure that all of the required features in the model are properly preprocessed and encoded where appropriate before the model is trained. Also, because the CatBoost algorithm is going to be run, which does not require encoding of categorical variables, that consideration is accounted for in the preprocessing step.

Algorithm 7 Preprocess Data

```
procedure PreprocessData(group_data, model_type = 'lgb')
    Extract month from group_data['month']
    group_data['month'] ← Convert to integer
    cat_cols ← {'material_sub_group', 'uom', 'month'}
    num_cols ← {'total_demand', 'standard_price', 'months_offset'}
    for each col in num_cols do
        group_data[col] ← Convert to float
    end for
    X ← group_data[num_cols + cat_cols]
    if model_type ≠ 'catboost' then
        for each col in cat_cols do
            dummies ← One-Hot Encode X[col] with prefix col
            X ← Concatenate X (after dropping col) and dummies
        end for
    end if
    Clean column names of X to remove special characters
    y ← group_data['sap_hist_consumption']
    return X, y
end procedure
```

Model Training and Testing

The following function was used train and test the models. A 80/20 time series split was used to demarcate the training and testing dataset. The hyperparameter tuning for each model were based on the hyperparmaters as defined in Table A.2. The model training was cluster based, models were built for BOM materials separately from non BOM materials. The function **evaluate_group** works as follows:

1. Extract features and target variable using the **preprocess_data** function.
2. Split the data into training and test sets using a predefined ratio.

3. Based on the **model_type**, select the appropriate parameter set.
4. Use GridSearchCV for hyperparameter tuning and train the model.
5. Predict on both training and test data to evaluate performance.
6. Return performance metrics such as MAE, MSE, RMSE, and R^2.

Performance Evaluation

The MAE, MSE, RMSE and R^2 score are used to evaluate the model performance for the five models used in training. The principles and formulas for these evaluation metrics have been described in Chapter 2. A summary of the performance evaluation results are shown in Table 3.4, based on the R^2 metric. The model with the best performance varies depending on the cluster data.

Table 3.4: Model Performance by Cluster

	Random Forest		Cat Boost		XG Boost		Light GBM	
cluster	train R^2	test R^2	train R^2	test R^2	train R^2	test R^2	train R^2	test R^2
GM0100	0.83	0.57	0.55	0.47	0.76	0.57	0.81	0.58
GM0200	0.94	0.73	0.80	0.72	0.98	0.74	0.93	0.76
GM0300	0.96	0.68	0.83	0.71	0.97	0.65	0.95	0.65
GM0600	0.87	0.59	0.79	0.70	0.95	0.73	0.90	0.67
GM0700	0.95	0.63	0.93	0.78	0.98	0.81	0.96	0.81
GM0800	0.97	0.73	0.85	0.65	0.90	0.72	0.97	0.74
GM1000	0.97	0.76	0.99	0.77	0.95	0.75	0.97	0.67
GM1100	0.95	0.78	0.88	0.51	0.95	0.75	0.97	0.73

3.2.4 Demand Normalisation using Forecast Error

The demand forecasting models work well for most clusters except for one cluster that represents about 22% of the materials, as a result of data gaps in the archive for that category. Therefore, a stop gap was developed for the material category and model that had sub-par performance. As earlier explained, the major demand forecasting happens at the finished drug product level, and that is cascaded down to the raw materials required. There have been instances of historical forecast inaccuracy at the FDP level which affects the raw material demand plan. Also, sometimes, the production schedule and defects increases or decreases the required raw materials.

Therefore, to mitigate these risks, the historical forecast accuracy, using the performance metric, mean absolute percentage error (MAPE), with the lead time offset for each material is used to normalise the future demand plan. MAPE is a measure used to assess the accuracy of forecasting methods in predicting values. It expresses the error as a percentage, making it easy to understand when comparing the accuracy of different models, especially when the scales of the datasets differ. MAPE is defined in Equation 3.1.

$$\text{MAPE} = \frac{100}{n} \sum_{t=1}^{n} \left| \frac{A_t - F_t}{A_t} \right| \tag{3.1}$$

where n represents the number of forecasted points, A_t is the actual value at time t, F_t denotes the forecasted value at time t, and $|\cdot|$ signifies the absolute value.

The normalisation is done in the following steps:

1. The historical demand plan for each month with the monthly offset (i.e., how many months in advance the demand was planned) is collated from the current month over the period of the lead time and smoothed out using exponential smoothing as defined in the Algorithm 8. This is done to capture the variability in the plan over the period of the lead time.

   In this algorithm,

   α is the filtered dataframe based on material_id, plant_id, and max_offset; and
   β is the resulting dataframe after applying the smoothing function.

2. The monthly forecast error is then calculated by deducting the smoothed forecast from the actual consumption.

$$\text{forecast\_error} = \text{SmoothedForecast} - \text{sap\_hist\_consumption} \tag{3.2}$$

3. The MAPE is then calculated over the period of the lead time of the material using the Algorithm 9.

   Here,

Algorithm 8 smooth_forecasts

procedure SMOOTH_FORECASTS(df, material_id, plant_id, max_offset)
  $\alpha \leftarrow$ Filter df for material_id, plant_id, and months_offset $\leq$ max_offset
  Sort α by months_offset and year_month
  if α is empty **then**
    return Empty DataFrame with columns year_month, SmoothedForecast, material, plant
  end if
  procedure EXP_SMOOTH(row)
    Set decay_rate to 0.5
    Calculate weight as decay_rate$^{\text{row[months_offset]}}$
    return weight $\times$ row[total_demand]
  end procedure
  Add WeightedForecast to α by applying exp_smooth
  Add Weight to α as $0.5^{\text{months\_offset}}$
  $\beta \leftarrow$ Calculate SmoothedForecast for each year_month in α
  Convert β to DataFrame with columns year_month and SmoothedForecast
  Add columns material and plant to β with values material_id and plant_id respectively
  return β
end procedure

α is the list containing tuples of calculated values for each row in the group,

β is the mean prediction value of the current row,

γ is the lead time in months, derived from the mean prediction,

δ is the starting month index for calculations,

ϵ represents absolute forecast errors for the current row,

ζ represents forecast errors for the current row,

η is the mean absolute percentage error for each forecast value,

θ is the average mean absolute percentage error, and

ι is the standard deviation of forecast errors.

4. The MAPE is then applied to adjust the demand plan.

The disadvantage of this approach is the normalised demand plan could be higher than the consumption. The historical error, even though it is based on the most recent period might not be an accurate representation of future errors especially for products that are in decline or growth lifecycles. However, this is only a stop gap until a future time when the data issues have been fixed and historical data can be used as a source of benchmark.

Algorithm 9 calculate_mape_and_std_dev

procedure CALCULATE_MAPE_AND_STD_DEV(group)
    Sort group by year_month
    Reset group's index
    Initialize an empty list α
    for each row in group **do**
        $\beta \leftarrow$ row's mean_prediction
        $\gamma \leftarrow \lceil \frac{\beta}{30} \rceil$
        $\delta \leftarrow \max(\text{index} - \gamma + 1, \text{group's minimum index})$
        $\epsilon \leftarrow$ absolute values of forecast_error from δ to index in group
        $\zeta \leftarrow$ forecast_error values from δ to index in group
        $\eta \leftarrow \frac{\epsilon}{\text{absolute value of row's sap\_hist\_consumption}}$
        $\theta \leftarrow$ average of $\eta \times 100$
        $\iota \leftarrow \zeta$'s standard deviation
        if length of ϵ is less than γ **then**
            flag $\leftarrow$ "incomplete"
        else
            flag $\leftarrow$ "complete"
        end if
        Append tuple to α with values: material, plant, year_month, SmoothedForecast, sap_hist_consumption, mean_prediction, prediction_std, γ, θ, ι, flag
    end for
    return DataFrame from α with specified columns
end procedure

3.2.5 Step 3: Multicriteria and Service Level Segmentation

Organisations typically save a large portion of their total investment via optimal inventory control. Inventory control does not just cover financial savings, it also covers space and manpower savings, and process simplification and transparency [66]. Typical methods used for inventory control include ABC, XYZ, VED, FSN, HML, SDF, GOLF, SOS as pictures in Figure 3-5 [61].

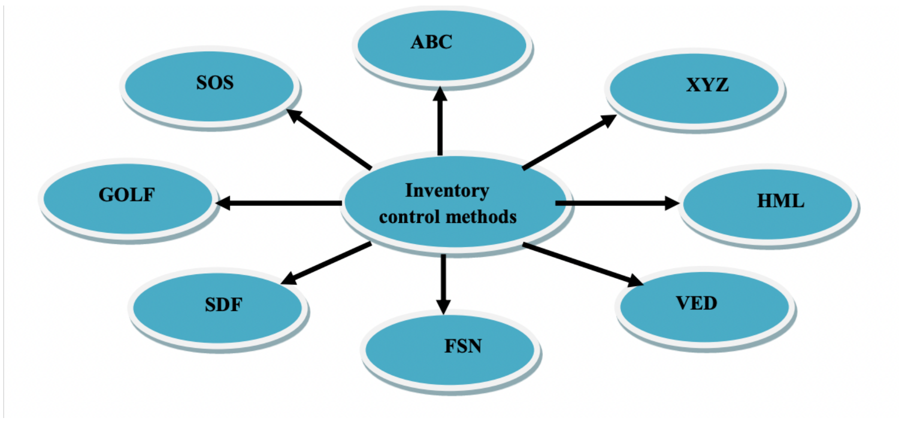

Figure 3-5: Inventory control Methods [66]

In order to decide which methods to use or how to combine them, it is important to understand the application and usage. A description of each method and its application is shown in Table 3.5.

Analysis Category	**Criteria**	**Application**
ABC	Annual Usage Value	Production Materials Classification
XYZ	Inventory investment	A category status
HML	Unit price	Manage high cost items
VED	Criticality	Managing inventory spare parts
FSN	Dispose non-moving inventory	Managing obsolescence
SDE	Sourcing Difficulties	Monitor availability and stock levels
GOLF	Procurement Source and procedure	Canalizing Agency can be used
SOS	Seasonality	Strategise purchase to buy in harvest season

Table 3.5: Inventory Control Methods

Inventory Control Methods

ABC Analysis

The ABC analysis, popularly known as Always Better Control [61] [27], is a widely used classification type that groups products and materials based on their frequency of usage and value. It is the most popular inventory control methodology adopted as Pareto's Law [61] [83]. The classification strategy is shown in Table 3.6. The annual consumption value is calculated as the multiplication of the annual demand and the item cost per unit. For A items, it is recommended that there is a close day to day control; for B items, periodic review; and for C items, infrequent review.

Category	% of Items	% of Annual Consumption Value	Control
A	About 15-20%	About 70%-80%	Maximum
B	About 30%	About 15%-20%	Moderate
C	About 50%-55%	About 5%-10%	Minimum

Table 3.6: ABC Classification [66][61][48]

XYZ Analysis

The XYZ approach is a dynamic extension of the ABC analysis [66]. The XYZ analysis helps to evaluate the fluctuations in demand. The coefficient of variation is used as a basis for this split and is typically 20% : 30% : 50% for $X, Y, Z,$ respectively.

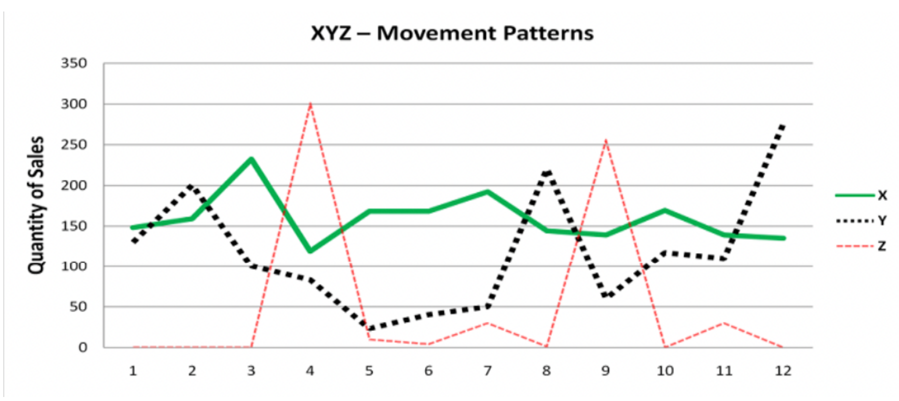

Figure 3-6: XYZ Patterns of Variability [83]

The X category includes materials that have low variability or fluctuations, the Y category describes materials that have substantial or medium fluctuations in demand, and the Z category is used for materials that have irregular and highly variable demand, as illustrated in Figure 3-6. The ABC-XYZ analyses are typically combined as shown in Table 3.7. The recommended inventory levels for the ABC-XYZ classification have been denoted in the Table 3.8.

	A	**B**	**C**
X	High Value Percentage Continuous Demand High Predictive Value	Average Value Percentage Continuous Demand High Predictive Value	Low Value Percentage Continuous Demand High Predictive Value
Y	High Value Percentage Fluctuating Demand Average Predictive Value	Average Value Percentage Fluctuating Demand Average Predictive Value	Low Value Percentage Fluctuating Demand Average Predictive Value
Z	High Value Percentage Irregular Demand Low Predictive Value	Average Value Percentage Irregular Demand Low Predictive Value	Low Value Percentage Irregular Demand Low Predictive Value

Table 3.7: ABC-XYZ Segmentation [66][83]

	A	**B**	**C**
X	Low Inventory	Low Inventory	Low Inventory
Y	Low Inventory	Medium Inventory	High Inventory
Z	Medium Inventory	Medium Inventory	High Inventory

Table 3.8: Recommended ABC-XYZ Classification Inventory Levels [83]

SDE (Scarce, Difficult, Easy) Analysis

The SDE methodology is used to classify materials or products based on their availability in the market. This helps facilitate and formulate appropriate procurement strategies based on each segment.

- **Scarce** - This includes items that are in short supply, single source, or are imported through government agencies. They are typically raw materials, spare parts, and imported items [61].

- **Difficult** - They are not easily available locally and have to be procured from distant places [61].

- **Easy** - These are items that are readily available and supply typically exceeds demands for these items [61].

HML (High, Medium, Low) Analysis

The HML methodology uses price to classify materials. To classify these items, they are tabulated in the descending order of their unit price. The HML analysis helps managers decide on their buying policies and ensures that more quantities of H and M items are not ordered due to their high price [61]. Their typical breakdown and composition is shown in Table 3.9.

Category	**Cost Scale**	**% of Items**
H	High	10% - 15%
M	Medium	20% - 25%
L	Low	60% - 70%

Table 3.9: HML Analysis [61]

FSN Analysis The FSN analysis method of classification is used to identify surplus/non-moving items and active items which have to be reviewed on a regular basis [61]. Here, F indicates fast moving, S indicates slow moving and N indicates non moving.

VED Analysis

The VED analysis is typically used for maintenance spare parts. Here, V stands for Vital, and is used to classify items for which non-availability cannot be tolerated and a large stock of inventory is required to be maintained. E (Essential) is used for items in which non-availability can be tolerated for a few days, and which have alternative sourcing. D (Desirable) is used to classify items whose non-availability can be tolerated for longer periods and would not cause an instant loss in production [61].

Applying Segmentation to Service Level

In many industries, such as information technology (IT) [83], Pharmaceuticals [26] [36] [12] [52] [31] [62], consumer goods [8] and automotive [33], multicriteria and multiple inventory control approaches have typically been used to manage inventory and improve operational efficiency from raw material to finished goods. Due to the peculiarity of the raw materials in the Amgen portfolio and how risk averse Amgen is, we define three criteria, leveraging the different inventory control methods in Section 3.2.5 and use them to segment the materials in order to determine appropriate service level (SL). The criteria are the variability, revenue impact, and

ABC segmentation. The breakdown of service level segmentation based on these criteria is shown in Table 3.10.

ABC Segment	Base SL.	Variability			Revenue Impact			Scarcity
		Low	Med	High	Low	Med	High	Y/N
A	95%	0%	+1%	+2%	0%	1%	+2%	99.90%
B	98%	-1%	0%	+1%	-1%	0%	+1%	99.90%
C	99%	-2%	-1%	0%	-2%	-1%	0%	99.90%

Table 3.10: Multi Criteria Segmentation for Amgen Raw Materials

The ABC segment represents the base service level. The variability and revenue impact factors serve as increments or decrements on the base service level. The mode in implementation is to cross reference variability and revenue impact with the ABC segment and apply the one increment that yields the highest service level. Further details about these criteria are discussed in the ensuing paragraphs.

ABC Segmentation: The ABC segmentation is based on the holding cost, which is the sum of the average yearly storage cost and the discounted cost of inventory.This percentile breakdown of each segment is shown in Table 3.11.

Category	Percentage
A	Top 10%
B	Second 10%
C	Remaining 80%

Table 3.11: ABC Segmentation for Amgen Raw Materials

Variability: The variability (low, medium and high) is defined using the lifecycle of the main finished drug product that the raw material is used for. The breakdown is delineated in Table 3.12.

Category	Phase
High	Launch
Med	Grow
Low	Defend, Decline

Table 3.12: Variability Designation for FDP Lifecycle

Revenue Impact: The revenue impact is based on the distribution in Table 3.13.

Category	Value USD
Low	< 500 Mln
Med	500 Mln - 1 bln
High	> 1 bln

Table 3.13: Revenue Impact Category for the Raw Materials

Scarcity: Some of the raw materials are custom or single sourced, which means that there is a greater risk and consequence of stock out, especially for the high revenue impact ones. These raw materials are being classified as scarce material, leveraging the SDE framework, and are designated to be at the highest service level, 99.90%, since the company cannot risk stocking out.

It is important to think of the service level segmentation as management's control lever to manage risk and variability. While Table 3.10 recommends a service level for a particular raw material, the ultimate decision rests with the management team to accept, reduce or elevate the level of risk of stock out for the raw material.

3.2.6 Step 4 and 5: Distribution Fitting and Monte Carlo Simulation

The outputs of the demand forecasting model, lead time forecasting model and service level segmentation are combined into a Monte Carlo simulation. Before the information is fed into the simulation, the distribution of demand is fitted during the period of the lead time. This is crucial because the safety stock Equation 2.4) is based on the assumption that demand follows a normal distribution. However, since not all raw materials have demand that neatly fits this pattern, we cannot directly apply the normal distribution model. Instead, we need to tailor the distribution model to each material's actual demand pattern during the lead time. Unlike traditional methods that often rely on the assumption of normally distributed demand, this approach recognizes that the demand patterns for raw materials can vary significantly and may not always follow a normal distribution. By fitting the demand distribution during the lead time period for each raw material individually, the unique characteristics and variability of demand are captured, ensuring a more accurate and realistic representation in the Monte Carlo simulation. This is accomplished using Algorithm 10.

The outputs of the demand forecasting model, lead time forecasting model and service level segmentation are combined into a Monte Carlo simulation.

Before the information is fed into the simulation, the distribution of demand is fitted during the period of the lead time. This is crucial because the safety stock Equation 2.4) is based on the assumption that demand follows a normal distribution. However, since not all raw materials have demand that neatly fits this pattern, we cannot directly apply the normal distribution model. Instead, we need to tailor the distribution model to each material's actual demand pattern during the lead time. This is accomplished using Algorithm 10.

Algorithm 10 Get Best Distribution

procedure GetBestDistribution($data$)
  $f \leftarrow$ Fitter($data$)
  Call f.fit()
  $best\_fit \leftarrow f$.get_best()
  ($best\_distribution\_name, best\_distribution\_params$) $\leftarrow$ first item of $best\_fit$
  return ($best\_distribution\_name, best\_distribution\_params$)
end procedure

The output of the distribution fitting of the demand over the lead time period, the lead time and variance data, and the service level are fed into the Monte Carlo simulation Algorithm 11. In this algorithm, ζ represents the confidence levels for safety stock calculation and ν represents the number of simulations in the Monte Carlo approach.

The output of the Monte Carlo simulation is the recommended distribution of the safety stock level.The cost benefit analysis can be performed to help management better understand the cost of stock out. Implementation of this would be demonstrated in Chapter 4.

Smoothing Safety Stock Target Changes

In practical inventory management, abrupt changes in safety stock targets from one month to another can be challenging to implement effectively. For example, if the safety stock target for a raw material is set at 100 units in month 1 and then reduced to 50 units in month 2, it may not be feasible to achieve this reduction immediately. The excess inventory that might have been been procured cannot be instantly eliminated and will remain in stock until it is consumed through normal production processes.

To address this practical limitation, a smoothing mechanism is created as an element of

Algorithm 11 Monte Carlo Simulation for Safety Stock

```
function MonteCarloSimulation(row, ν = 1000)
    ζ ← [90, 95, 97, 98, 99.9]
    Initialize results map with ζ as keys and empty lists as values
    if row['best_distribution_params'] is None or equals '0' then
        return None
    end if
    for sim = 1 to ν do
        random_lead_time_mean ← RandomNormal(row['Mean'], row['Std'])
        distribution_name ← row['best_distribution_name']
        distribution_params ← ConvertStringToOriginal(row['best_distribution_params'])
        Print "Error occurred with parameters"
        return None
        distribution ← GetDistribution(distribution_name)
        if distribution_params is a dictionary then
            dist_sample ← DistributionSampleWithParams
            dist_std ← DistributionStdWithParams
            random_forecast_mean ← dist_sample(distribution, distribution_params)
            demand_std ← dist_std(distribution, distribution_params)
        else
            dist_sample ← DistributionSampleWithArgs
            dist_std ← DistributionStdWithArgs
            random_forecast_mean ← dist_sample(distribution, distribution_params)
            demand_std ← dist_std(distribution, distribution_params)
        end if
        demand_std ← row['forecast_std']
        for each z in ζ do
            lead_term ← max(0, random_lead_time_mean) × demand_std^2
            forecast_term ← max(0, random_forecast_mean)^2 × row['Variance']
            safety_stock ← z-percentile × sqrt(lead_term + forecast_term)
            Append safety_stock to results under key z
        end for
    end for
    return results
end function
```

the proposed methodology. The smoothing process aims to gradually adjust the safety stock targets over time, avoiding drastic changes that may be difficult to implement in real-world scenarios. By considering the previous month's safety stock level and the current month's target, the smoothing mechanism calculates a more achievable safety stock value for each month. The smoothed safety stock target for a given month is determined using Equation 3.3.

$$\text{smoothed\_ss\_target} = \alpha \times \text{current\_month\_target} + (1 - \alpha) \times \text{previous\_month\_ss} \quad (3.3)$$

where α is a smoothing factor between 0 and 1, which determines the weight given to the current month's target and the previous month's safety stock level. A higher value of α gives more weight to the current month's target, while a lower value of α gives more weight to the previous month's safety stock level.

This smoothing approach ensures a more gradual transition between safety stock targets, aligning with the practical constraints of inventory management. It allows for a more realistic implementation of the proposed methodology, considering the limitations of reducing excess inventory levels instantaneously.

The smoothing mechanism has some limitations that may impact its effectiveness in real-world scenarios over time. The effectiveness of the smoothing mechanism is also heavily dependent on the choice of the smoothing factor α. There is also a potential risk of over-smoothing. To address these limitations, adaptive smoothing factor that adjusts based on the magnitude and direction of changes, incorporating external factors can be implemented. The smoothing parameters needs to be monitored and adjusted over time. The efficacy of the mechanism can also be improved when combined with safety stock optimization models, like the model that is described in Step 4. The methodology is however designed to allow the team have the capability to decide whether or not to use the smoothing mechanism for the Monte Carlo simulation results.

3.3 Disruption/What-If Framework

Managing a multiechelon supply chain internal and supply risks is already a herculean task. However, in the event of a disruption, it becomes an almost impossible task as the sustainability of the supply chain could be compromised due to reactive measures to the disruption [24]. Major disruptions that have negatively affected most industries across the globe include massive floods, chemical explosions, industrial strikes, extreme winters [24], and most recently the COVID pandemic. The COVID-19 and lockdown measures resulted in increased demand of domestic products. This led to the bullwhip effect, especially for companies and industries that had not succeeded in predicting the increase in demand [63]. In order to mitigate or manage such disruptions and help the company make more informed decisions to minmize stock outs, a framework is developed to guide the company through such scenarios.

The disruption simulation framework is designed to manage inventory and safety stock levels in the event of potential disruptions, such as pandemics or natural disasters. This framework extends beyond existing studies by explicitly modeling the interactions and dependencies between raw materials. While previous works often treat raw materials in isolation, this framework captures the complex network of relationships and potential cascading effects of disruptions. By incorporating supply chain network dynamics and considering the propagation of risks across multiple tiers, the simulations provide a more realistic and comprehensive assessment of the impact of disruptions on inventory levels and overall supply chain performance. The disruption framework is delineated in the following steps.

Step 1: Risk Identification

- **Supplier Failures:** Identifying risks associated with the failure of suppliers, which could be due to financial troubles, operational issues, or external events affecting the supplier's ability to deliver. Maintaining a risk register can help with this. Amgen already has a risk management team that helps with risk identification.

- **Pandemics & Natural Disasters (Black Swans):** Recognizing the potential for rare but high-impact events like pandemics and natural disasters that can disrupt operations in unpredictable ways.

Step 2: Risk Assessment

- **Leverage COVID data to provide historical maximum lead times:** Using data from the COVID-19 pandemic to understand the worst-case scenarios for supplier lead times.

- **Use Risk Matrix to quantify potential impact and likelihood (range of probabilities):** Employing a risk matrix to evaluate the severity of potential impacts and their probabilities, providing a structured approach to risk assessment.

Step 3: Monte Carlo Simulation

- **Use output of risk assessment (probabilities and impact):** Utilize the output of the risk assessment to as inputs into the Monte Carlo simulation, such as the likelihood of certain events and their potential impacts on lead time.

- **Run the simulation for each scenario and record the results:** Perform the simulation across various scenarios to understand the cost and volume implications and the likelihood of stock out, helping to understand the range of potential outcomes.

This can be implemented using the Algorithm **??**, where ζ represents the confidence levels for safety stock calculation, ν represents the number of simulations in the Monte Carlo approach, π represents the probability of a disruption and ξ represents the potential impacts of disruptions.

Step 4: Stochastic Programming (optimal safety stock level)

- Determining the decision variable (safety stock level).
- Objective function (minimize holding stock & minimize lost sales).
- Defining clear constraints (service level for each disruption scenario).

Algorithm 12 Disruption Monte Carlo Simulation for Safety Stock

function DisruptionMonteCarloSimulation(row, $\nu = 1000$, $\pi = 0.4$, $\xi = [1, 1.2, 1.5]$)
    $\zeta \leftarrow [90, 95, 97, 98, 99.9]$
    Initialize results map with ζ as keys and empty lists as values
    if row[‘best_distribution_params’] is None or equals ‘0’ **then**
        return None
    end if
    for sim = 1 to ν **do**
        random_lead_time_mean ← RandomNormal(row[‘Mean’], row[‘Std’])
        random_lead_time_std ← $\sqrt{\text{row[‘Variance’]}}$
        distribution_name ← row[‘best_distribution_name’]
        distribution_params ← ConvertStringToOriginal(row[‘best_distribution_params’])
        Print “Error occurred with parameters”
        return None
        distribution ← GetDistribution(distribution_name)
        if distribution_params is a dictionary **then**
            random_forecast_mean ← DistributionSampleWithParams(distribution, distribution_params)
        else
            random_forecast_mean ← DistributionSampleWithArgs(distribution, distribution_params)
        end if
        demand_std ← row[‘forecast_std’]
        disruption_event ← RandomUniform(0, 1)
        if disruption_event $< \pi$ **then**
            disruption_impact ← RandomChoice(ξ)
            random_lead_time_mean $\times =$ disruption_impact
            random_lead_time_std $\times =$ disruption_impact
        end if
        for each z in ζ **do**
            variance_factor ← max(0, random_lead_time_mean) $\times$ demand_std^2 + max(0, random_forecast_mean)^2 $\times$ random_lead_time_std^2
            safety_stock ← z percentile value $\times$ $\sqrt{\text{variance\_factor}}$
            Append safety_stock to results under key z
        end for
    end for
    return results
end function

Optimization Algorithm for Amgen Use Case

The main aim of the optimization algorithm is to minimize the total cost associated with a particular level of safety stock, while ensuring that the safety stock is greater than or equal to the maximum possible demand. The optimization problem is formulated as:

$$\begin{aligned} \underset{S_{zi}}{\text{minimize}} \quad & C(S_{zi}) = h \times S_{zi} \\ \text{subject to} \quad & S_{zi} \geq D_{\max}, \quad \forall z \in Z, i \in \{1, 2, \ldots, 1000\} \end{aligned}$$

where: h is the holding cost per unit,

$D_{\max}$ is the maximum possible demand,

Z represents a list of possible confidence levels '[90, 95, 97, 98, 99.9]',

S_{zi} is the safety stock for the ith simulation at z confidence level, and

$C(S_{zi})$ represents the total cost of holding a safety stock level S_{zi}.

Step 5: Risk Mitigation

The following are risk mitigation strategies in the event of a disruption.

- **Segmentation:** Categorizing inventory or suppliers to prioritize actions.
- **Communicate More:** Improving communication channels within the supply chain for better coordination and faster response to changes.
- **Diversification:** Reducing reliance on single sources and diversifying suppliers to mitigate the impact of any one supplier failing.
- **Visualisation:** Using visual tools to better understand and communicate risks and their potential impacts on the supply chain to upper level management.
- **Production Plan changes:** Adjusting production plans to be more resilient to disruptions, for example by increasing flexibility or capacity.

Chapter 4

Implementation of Methodology and Results

The goal of this project is to determine the optimal safety stock to be held for different raw materials at every point in time in the organisation. The different sources of variability such as lead time and demand variability that affect the volume of safety stock to be held have been discussed in Chapter 1. This chapter shows how data-driven methodologies discussed in Chapter 2 and the models trained in Chapter 3 have been implemented to determine safety stock for select raw materials, and discusses the implication for the overall supply chain for Amgen.

4.1 Safety Stock Determination: Test Cases

There are over 10,000 raw materials that are managed by the Amgen supply chain team. These raw materials have been categorized and segmented as shown in Chapters 2 and 3. To demonstrate how the proposed methodology runs and the impact of the proposed methodology versus the old methodology used by Amgen, a set of test cases are considered.

4.1.1 Test Case 1: Raw Material A with Short Lead Time

This Raw material A is selected due to its short lead time of circa 40 days, to demonstrate how important changes in decisions made by the organisation in how much safety stock should be held can have a significant impact on savings and inventory control compared to status quo. The raw material details are shown in Table 4.1.

Parameter	**Details**
Material Category	Serum/Media (GM1100)
Material Description	Drug Substance Media A
Number of Finished Drug Products	23
Manufacturing Plants Using It	5
Lifecycle of Main Finished Drug Product	Decline
Holding Cost Segment	A (Top 10%)
Revenue Impact	High
Variability	Low
Unit of Measurement	milliliter (ml)
Current Company Safety Stock Policy	6 Months Forward Coverage plus buffer

Table 4.1: Raw Material A Details

Current Demand Plan

Figure 4-1 represents the demand plan of this raw material as of February 2022. It is important to note that this raw material has a lead time of about 40 days, which means it has a relatively shorter response period, and the demand plan is updated monthly in the system. Therefore, changes in the demand for future months are updated subsequently to capture any variability. The figure also shows the actual consumption, with company safety stock at six times the demand plan of the raw material (6 MFC). This raw material has relatively low variability and with a shorter lead time, one could say the six months forward coverage safety stock plan with buffer is an overkill.

Simulation Results

A test is run on the same historical demand plan of February 2022 to compare how the methodology performs with the company's methodology for safety stock. The demand is run through the models trained in Chapter 3 and fitted during the lead time period using

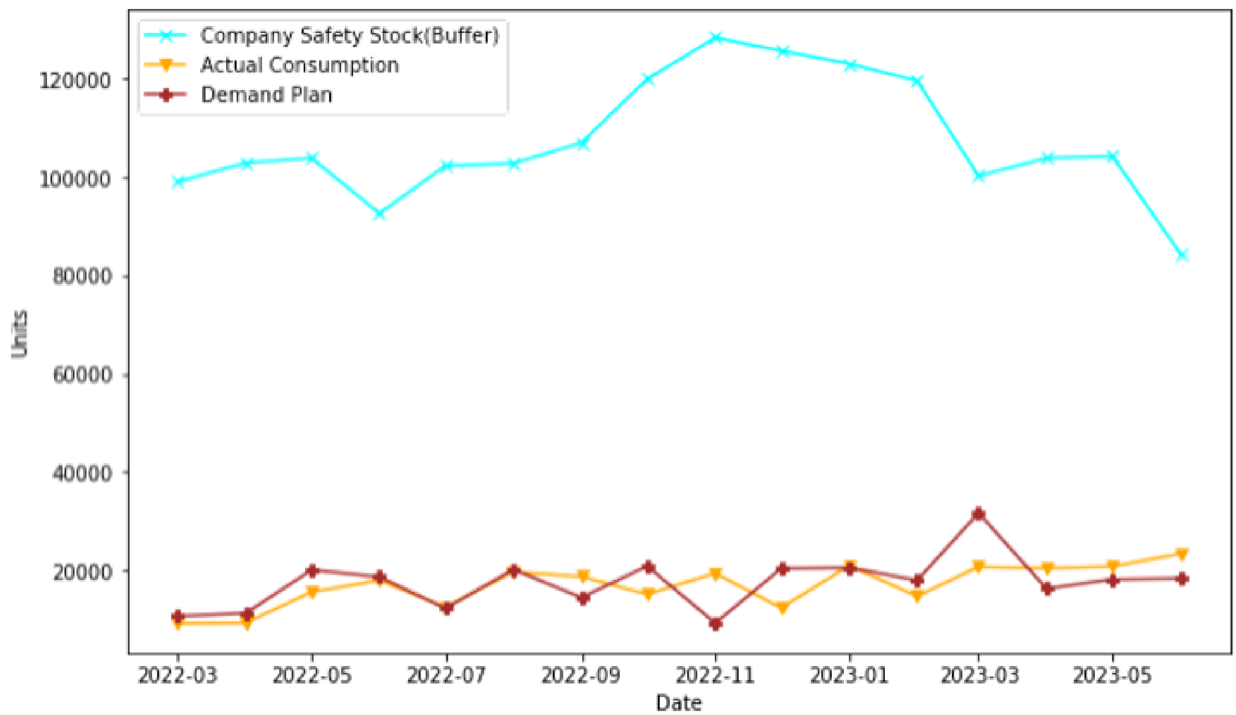

Figure 4-1: Raw Material Plan, Actual Consumption and Safety Stock for Material A

the lead time and variance predicted using models as also trained in Chapter 3. This test is run at different service levels, 90%, 95% and 97%, to understand the differences between the output for each service level. The results are shown in Figure 4-2.

The box plots in Figure 4-2 represent the recommended safety stock levels based on the results of the implementation of the methodology proposed in Chapter 3. For each time period, there are differences in quantities between the results of the simulation at 90%, 95% and 97% service level due to the magnitude of the service level z-scores. However these differences are not glaring due to the short lead time of this raw material and the variance of the prediction in that time period.

The characteristics of this material shows that this raw material falls in the top 10% holding stock category based on the segmentation framework presented in Section 3.2.5. It also has a high revenue impact and relatively low variability. Based on the recommended service level segmentation framework, the service level is proposed to fall between 95% and 97%.

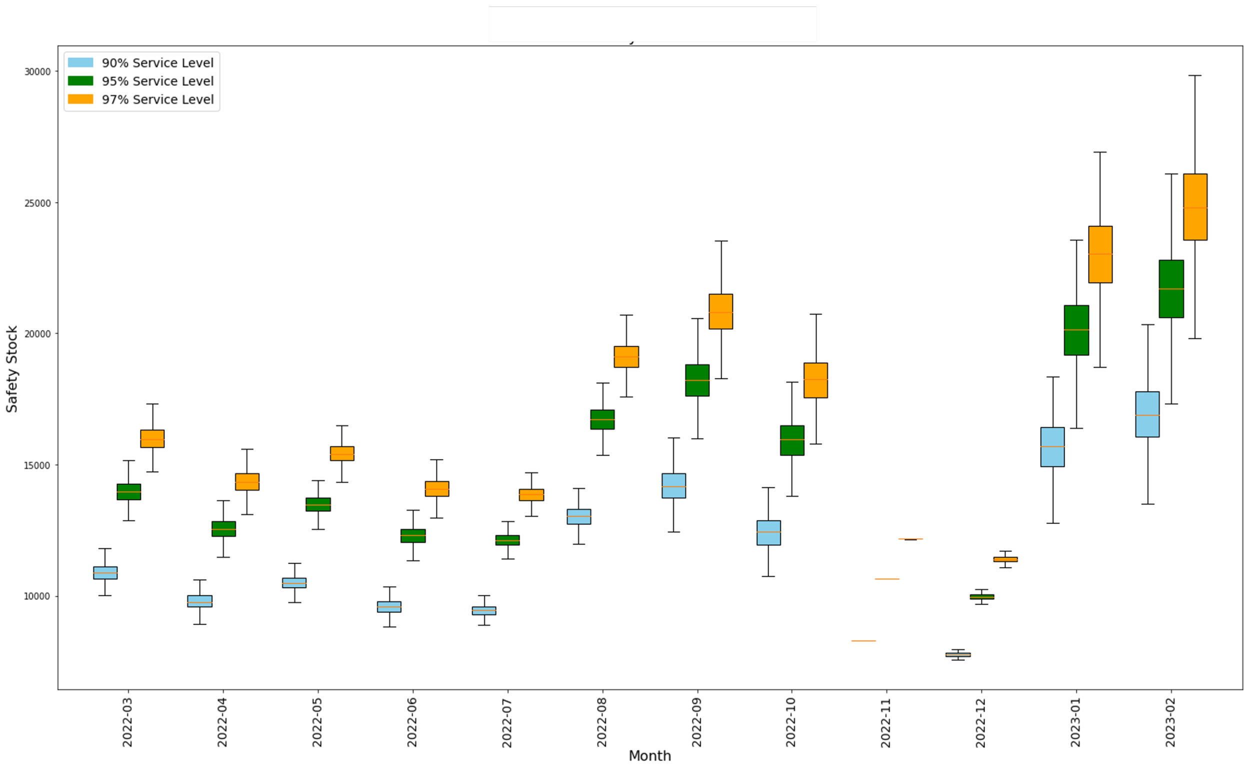

Figure 4-2: Box Plots of Simulation Results of Safety Stock at Different Service Levels for Material A

Comparison with Company Safety Stock

Further diving into the results and using the 95th percentile of the box plots (the upper whiskers) for both the 95% and 97% service levels results, the simulated safety stock is compared the company safety stock, actual consumption, and demand plan in Figure 4-3. This helps to check if there is any risk of stock out using the new model results, and also compare the model and company safety stock levels.

The demand plan which is also the cycle stock, is not so variable. Comparing the model outputs at both 95% and 97% service levels with the actual consumption, the plot shows that the model safety stock is more than enough to cover any changes in demand during that period. It is also important to note that the model further refines its output when tested on the demand plan for the next planning period, as the demand plan is updated monthly. Raw materials with a short lead time period like material A, would have short recovery periods, as errors in demand for months outside the lead time period can be adjusted using both the machine learning model and the monthly update of the demand plan.

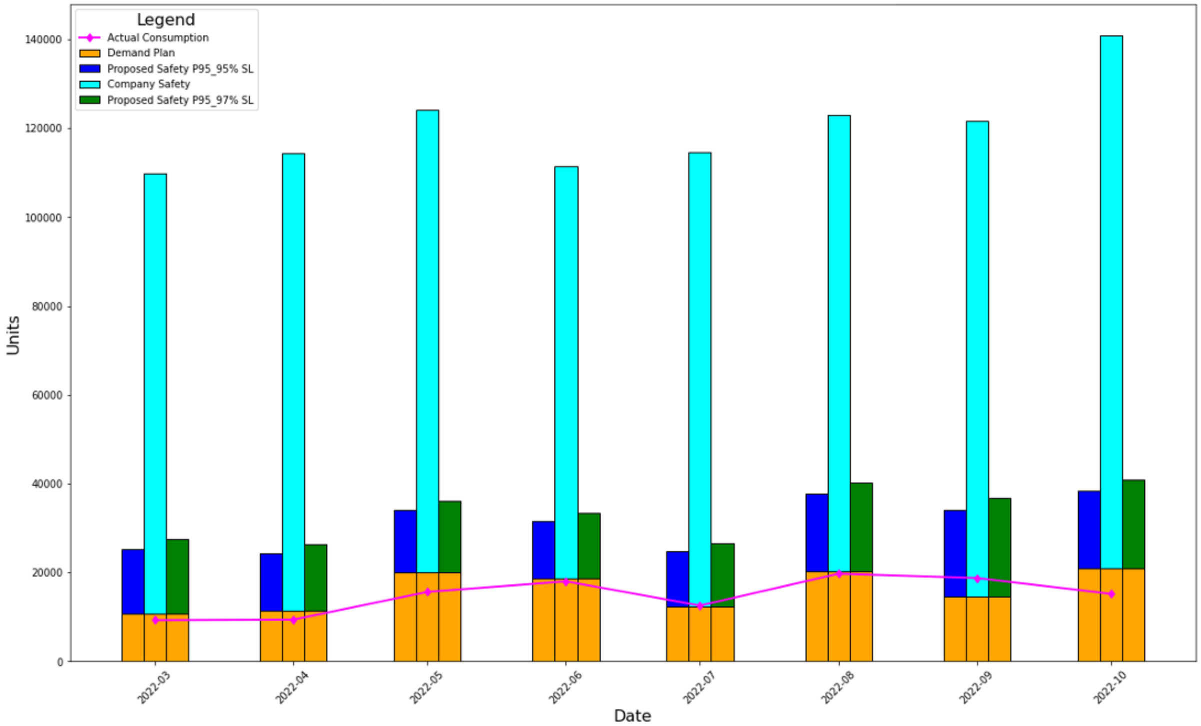

Figure 4-3: Comparison of Model Safety Stock with Company Inventory Levels for Material A

Cost Impact

It is important to understand the cost implication of the company's policy versus the model outputs, in terms of inventory value. Comparing the proposed safety stock levels by the model, the results show that the company has been sinking excess money into purchasing unrequired stock of inventory, shown in Figure 4-4, which is essentially the holding cost of inventory. We see the cost of this excess inventory shows that the company could have saved up to \$1.5 million monthly on cost of procurement of this raw material. Note that this does not account for holding cost in warehouses, which signifies more working capital being expended on inventory purchasing.

There are two key elements of holding cost. The first element is the cost of capital of the cash "tied up" in inventory. The cost of capital used will vary over time but typically can be in the range of 8-10%. The second element is the cost of warehouse space, which can be estimated by the average cost of leasing external warehouse pallet positions. Making the right inventory management decisions is important to ensuring a sustainable supply chain in

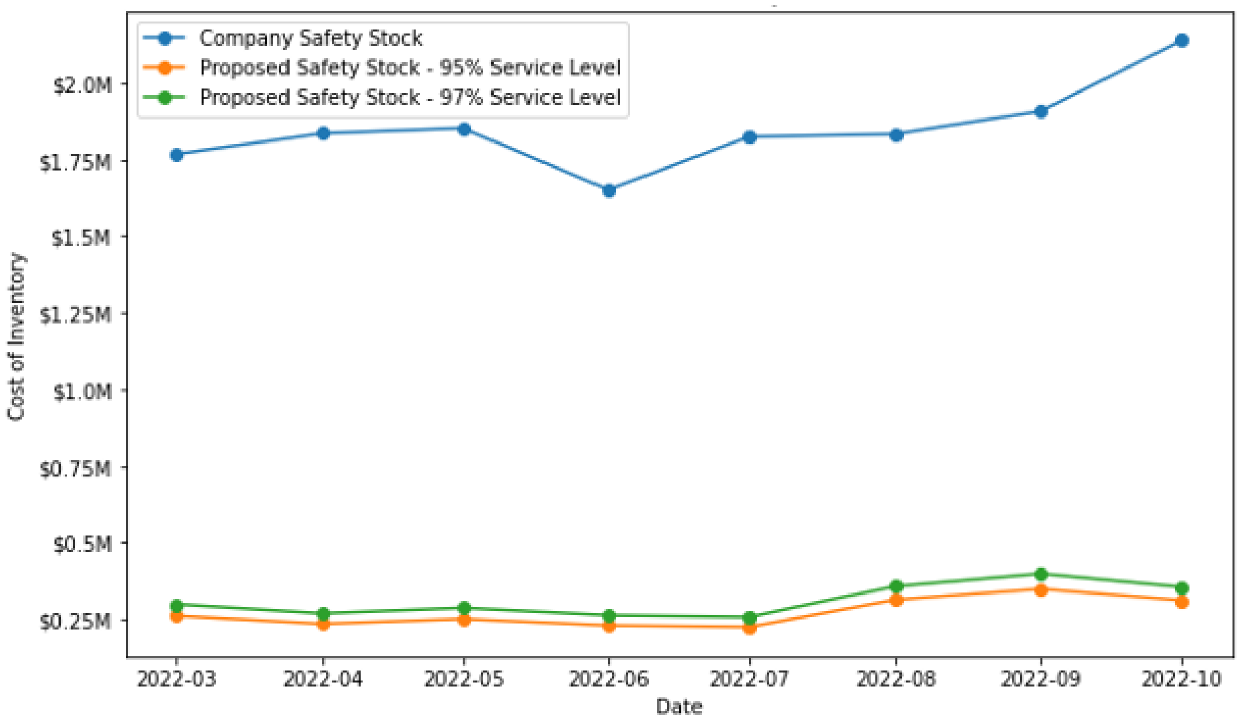

Figure 4-4: Safety Stock Cost Impact for Material A

the long run.

4.1.2 Test Case 2: Raw Material B with Long Lead Time

Raw material B is next selected as a test case due to its long lead time of about 11 months and its criticality in Amgen's supply chain. The parameters in Table 4.2 describe this raw material.

Current Demand Plan

Figure 4-5 shows the demand plan of the raw material as at February 2022. This raw material has a lead time of about 348 days, which means it has a relatively longer response period compared to that of raw material A due to its longer lead time. The demand plan of this material is also updated monthly in the system. Therefore, any changes in the demand for future months are updated subsequently to capture variability.

However, this raw material has very medium to high variability as demand plan actual consumption in some months are 0 (see months May to August 2022 in Figure 4-5). De-

Parameter	Details
Material Category	Filter (GM0600)
Material Description	Filter B
Number of Finished Drug Products	3
Manufacturing Plants Using It	5
Lifecycle of Main Finished Drug Product	Grow
Holding Cost Segment	A (Top 10%)
Revenue Impact	High
Variability	Medium
Unit of Measurement	Each (EA)
Current Company Safety Stock Policy	8 Months Forward Coverage plus buffer

Table 4.2: Raw Material B Details

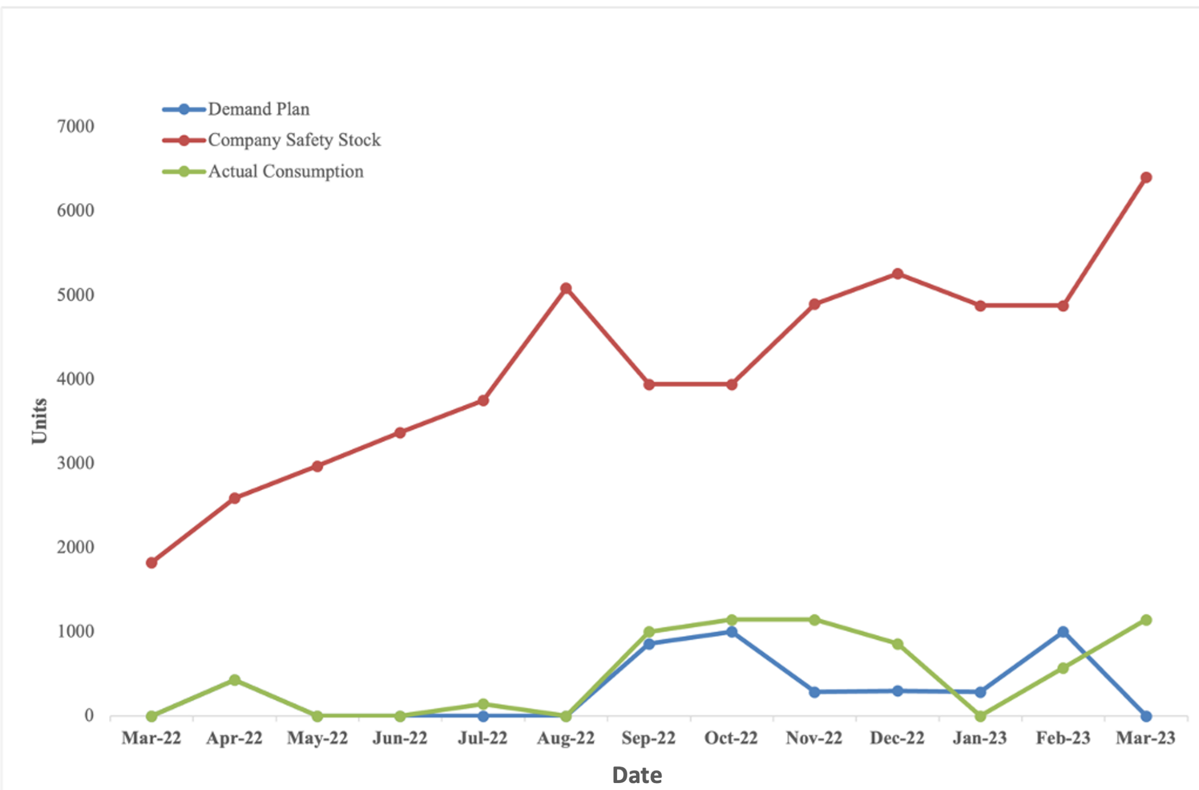

Figure 4-5: Demand Plan, Actual Consumption and Safety Stock for Material B

termining the safety stock for such a material is challenging and using a judgment based approach could result in underestimating or overestimating how much stock is required which could result in stockouts, especially with its long lead time.

Simulation Results

A test is run using historical data to compare how the new methodology performs, compared with the company's methodology for safety stock. The simulation is run similar to the process utilized for Test Case 1. The results are shown in Figure 4-6

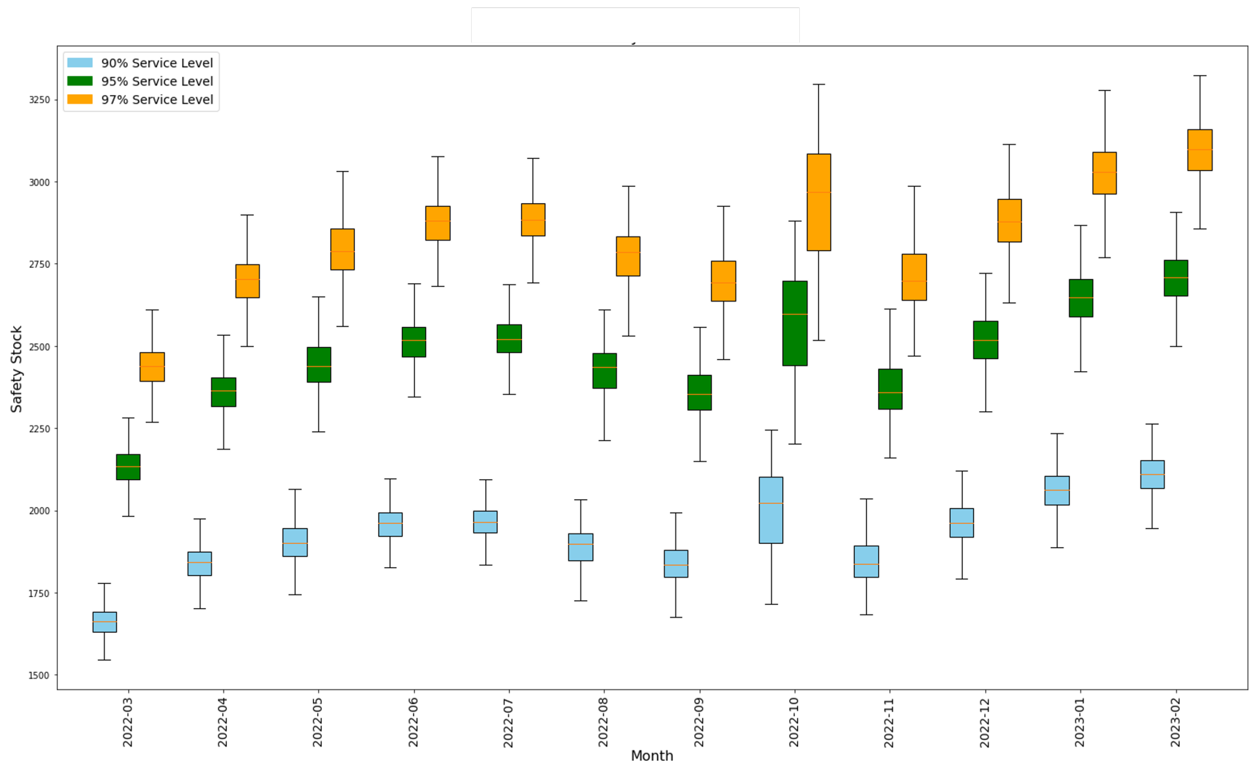

Figure 4-6: Box Plots of Simulation Results of Safety Stock at Different Service Levels for Material B

The box plots in Figure 4-6 represent the safety stock levels based on the results of the Monte Carlo simulation. There is a wide range of values for each of the box plots, and a significant difference between the results across the different service levels compared to that of Test Case 1, due to the long lead time and variability of this material. To further explain this, the histogram for the simulation results for July 2022 is shown in Figure 4-7.

The segmentation framework delineated in Chapter 2 shows that this raw material falls in the top 10% holding stock category; it also has a high revenue impact and medium variability.

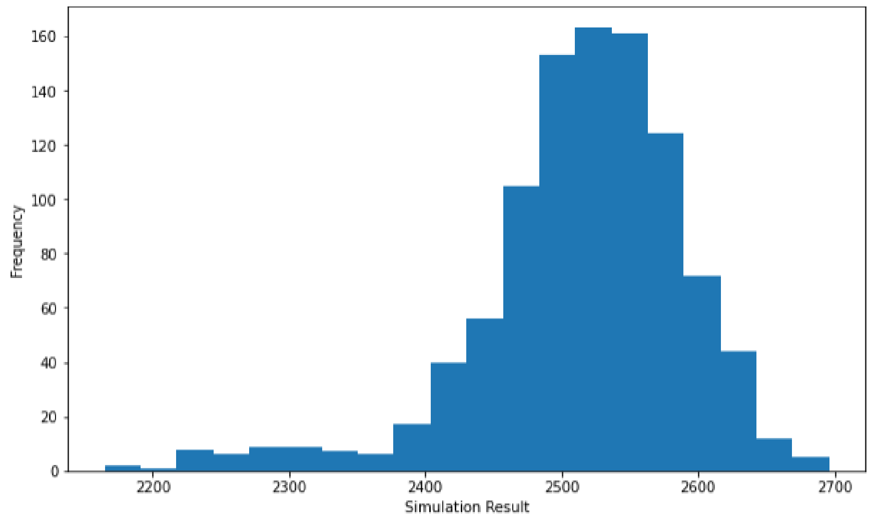

Figure 4-7: Stochastic Safety Stock for Material B - July 2022 at 95% Service Level

Based on the segmentation framework put together, the service level is proposed to fall between 95%, 96% and 97%.

Comparison with Company Safety Stock

To further analyze the results, the 95th percentile of the box plots for the 95% and 97% service levels is examined. The simulated safety stock is then compared to the company's safety stock, as shown in Figure 4-8.

The demand plan for this raw material is highly variable. Comparing the model outputs at both 95% and 97% service levels with the actual consumption, Figure 4-8 shows that the model safety stock was more than enough to cover any changes in demand during that period. However, due to the long lead time for this material, the model results are significantly higher than the demand plan to account for any possible lead time variability and variability in demand during the lead time. It is also important to note in Figure 4-8 that the model simulated higher safety stock than what the company policy was in March 2022 (for instance) based on the data-driven approach utilised by the model. This also demonstrates the fact that the model does not always give a lower volume than what the company policy is, but rather utilizes data and takes into account the variability in demand, and the value and variance of the lead time, at the point of forecast to estimate what the safety stock should be. This supports the credibility and efficacy of the proposed methodology.

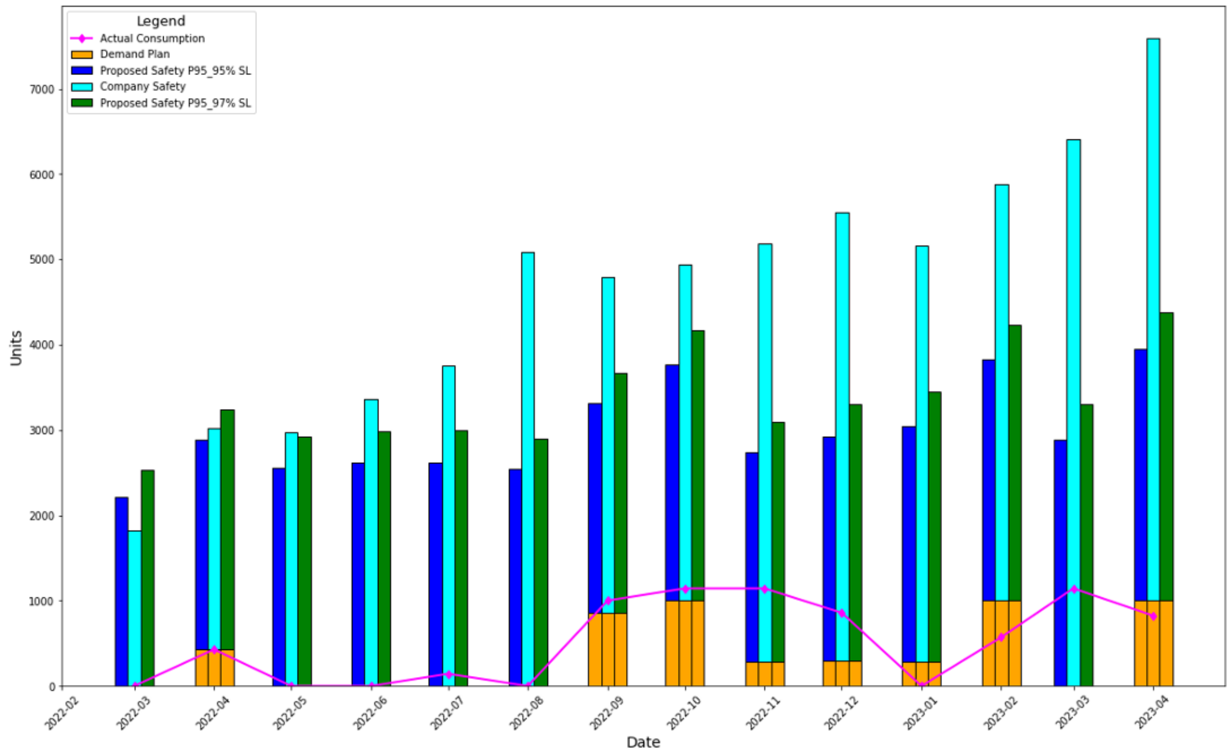

Figure 4-8: Comparison with Company Inventory Levels for Material B

Cost Impact

This material is in the top 10% of materials in terms of holding cost rate (i.e. "A" segment). Figure 4-9 shows the cost impact when comparing the company safety stock with the simulated safety stock at 95% and 97% service levels and this indicates that Amgen had excess safety stock of about $1 million for this raw material.

4.2 Disruption Analysis

Managing a multi-echelon supply chain's internal and supply risks is a challenging task, which becomes even more difficult in the event of a disruption that threaten its sustainability. Such disruptions include events such as floods, strikes, extreme weather, and the COVID pandemic. To address this, a disruption simulation framework is created, as described in Section 3.3. The disruption simulation framework is applied to raw material A. Supply disruption risks with probabilities of 40% and 80%, and lead time low, medium and high impact of 1x, 1.2x

Figure 4-9: Safety Stock Cost Impact for Material B

and 1.5x the base lead time, is simulated on the raw material safety stock levels. Figure 4-10 shows the results of the simulation under these conditions.

In each iteration of the disruption simulation algorithm, it samples random values for lead time mean and standard deviation based on the input data. It also checks if a disruption event occurs and if yes, it applies a random disruption impact to the lead time. Because of the way the algorithm runs, it does not just assume a multiplicative effect when the probability is increased from 40% to 80% as shown in Figure 4-10. Instead, a more refined estimate of impact is seen. This simulation capability will help the company to adapt and understand the impact of possible risks and scenarios.

4.3 Projected Business Value of Project

In the ever-evolving landscape of global business, maintaining an efficient and responsive inventory system is paramount. This project represents a novel step towards redefining the approach to safety stock determination. By harnessing the predictive power of machine

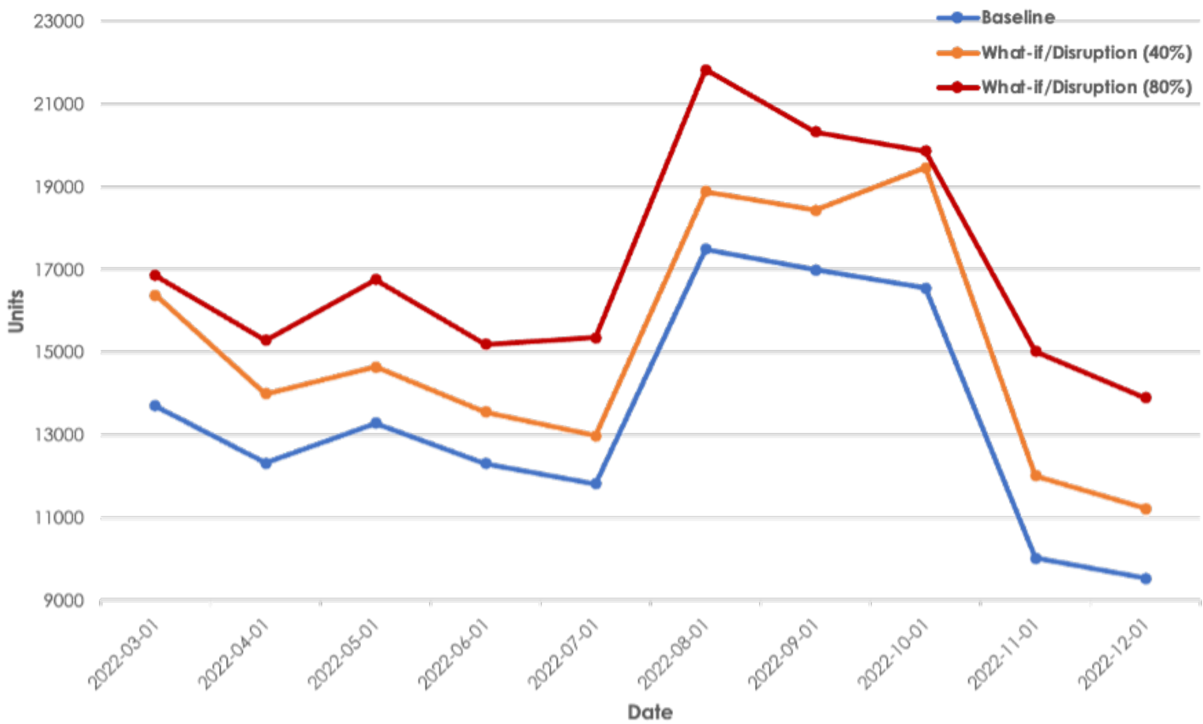

Figure 4-10: Disruption Simulation for Safety Stock of Material A at 95% Service Level

learning and the robust analytical capabilities of stochastic simulation, this initiative promises to deliver substantial business value. It not only offers a significant reduction in inventory costs but also provides a resilient framework for managing supply chain disruptions. The benefits that a data-driven strategy affords Amgen, and by extension, other companies in the biotechnology industry where there are grave implications of stock outs are profound. The approach is also scalable to other industries.

Cost Savings through Reduced Target Inventory

By using data-driven approaches to predict demand and optimize safety stock levels, there can be significant cost cutting. Based on a subset of about 50 materials, Amgen can achieve a minimum of 25% in holding cost savings. This optimization reduces holding costs and capital tied up in inventory, enabling the allocation of resources to other value-generating activities.

Enhanced Supplier Management with Historical Data Insights

The integration of historical data into machine learning models allows for the anticipation and planning of supply chain disruptions. The lead time models developed also help predict lead times based on historical performance of the supplier, which will be instrumental in supply and procurement planning, and mitigate lead time variability risks. The simulation of various scenarios provides Amgen with improved supplier management capabilities, reducing the impact of potential future disruptions. This proactive approach can enhance the reliability of the overall supply chain.

Realistic Demand Distribution Assumptions

Traditional inventory management methods often incorrectly assume a normal distribution of demand. The proposed methodology utilizes key data packages to identify the true demand distribution, which may be non-normal. Stochastic simulation then applies these distributions, yielding more realistic and accurate results that better reflect demand variability.

Informed Decision-Making with Cost Implication Analysis

This project facilitates strategic decision-making by providing a clear understanding of the cost implications associated with different inventory scenarios. Managers are empowered to make informed decisions that align with the company's financial goals, considering the trade-offs between holding costs and the risk of stock-outs.

Industry and Production Level Adaptability

The methodologies developed in this project are applicable across a wide range of industries and production levels such as the drug substance, drug product and finished drug product. The adaptability of machine learning and stochastic simulation means that the models can be tailored to meet the unique demand and supply dynamics of various business operations.

Utilization of Existing Infrastructure

The data-based approach can be integrated with current IT infrastructure, utilizing existing data systems and processes such as data lake and SAP. This means that Amgen can leverage their current data systems and processes to feed into the models, allowing for a more seamless implementation and reducing the need for additional investments in new infrastructure.

4.4 Challenges and Drawbacks of New Methodology

The new methodology for safety stock determination combines machine learning models for demand and lead time forecasting with Monte Carlo simulation and multi-criteria segmentation. While this approach offers several benefits and business value (refer to Section 4.3) such as improved accuracy, cost savings, and risk mitigation, there are some challenges and potential drawbacks. These drawbacks are discussed, along with potential mitigation strategies that are and can be implemented.

Complexity and Interpretability

Advanced machine learning models, such as CatBoost, can capture complex patterns and relationships in the data, leading to improved predictive performance. However, this complexity often comes at the cost of interpretability. These models may be perceived as a "black box," where the internal workings and decision-making process are not easily understandable by business stakeholders. This lack of interpretability can pose challenges in building trust and adoption of the methodology. Stakeholders may be hesitant to rely on a model they do not fully comprehend, especially when it comes to critical decisions like inventory levels.

To mitigate this challenge, efforts are made to enhance the models' interpretability. Techniques like feature importance analysis are applied to identify the key factors influencing the models' predictions. This provides stakeholders with valuable insights to better understand the outputs. In addition, clear documentation are developed to help stakeholders understand the inputs, outputs, and limitations, promoting transparency and building trust in the methodology.

Robustness across diverse materials

Amgen's vast portfolio of raw materials encompasses a wide range of characteristics, demand patterns, and supply chain dynamics. The proposed methodology must demonstrate robustness and reliability across this diverse spectrum of materials. A one-size-fits-all approach may not suffice, as the model's performance could vary depending on the unique attributes of each material.

To ensure robustness, extensive testing and validation across a representative sample of materials is done. This process not only involved assessing the models' performance on historical data but also stress-testing it under various scenarios and assumptions. By rigorously evaluating the model's behavior across different material categories, the team is able identify potential weaknesses and take steps to address them.

One approach incorporated in the methodology is the development of specialized models for different material categories. By tailoring the model architecture, feature selection, and hyperparameters to the specific characteristics of each category, the system can better capture the nuances and complexities of diverse materials. This modular approach allows for fine-tuning and optimization based on the unique requirements of each group.

Furthermore, the models developed incorporate a wide range of relevant data sources can help improve the model's robustness. In addition to historical demand and supply data, the models consider factors such as supplier performance and external events (disruption simulation framework). Future work can incorporate market trends and regulatory changes that may impact material availability.

Continuous monitoring and feedback loops are also critical for maintaining the methodology's robustness over time. As new data becomes available and business conditions evolve, the models should be regularly updated and retrained.

Subjectivity in Risk Quantification

The disruption simulation framework provides a valuable tool for testing the impact of different risk scenarios on inventory levels and costs. However, precisely quantifying the likelihood and impact of various risks remains challenging and subjective.

To address this, the methodology leverages a combination of historical data and expert judgment to simulated quantified risks. Collaborating with the risk management team, suppliers, and other stakeholders to gather relevant data and insights is important to ensure robustness of quantification. In addition, sensitivity analysis should also be performed to understand how changes in risk assumptions affect the simulation results. This can help identify the most critical risks and prioritize mitigation efforts accordingly.

Management Trust and Acceptance

Even if technical measures are in place to control for variability and ensure model robustness, a significant barrier to the implementation of machine learning models is gaining the trust of management and decision makers. Overcoming this trust hurdle requires not only technical solutions but also strategic communication and education efforts to demonstrate the reliability and benefits of these models. A multi-pronged and phased approach to manage this is discussed in Chapter 5. In addition, establishing robust governance and monitoring mechanisms is critical. Clear policies and procedures should be put in place to ensure the models' outputs are regularly reviewed, validated, and adjusted as needed. Showcasing the tangible benefits and success stories of the methodology can help overcome the psychological barriers.

In summary, this project offers a technologically advanced solution to optimize inventory and safety stock levels, ultimately leading to enhanced operational efficiency and improved bottom-line performance. The business value derived from this project is manifested in cost savings, improved supply chain resilience, and enhanced decision-making capabilities, which are applicable across various industries. Key drawbacks of this methodology are discussed and mitigation strategies identified. Other operational improvements that will be beneficial to ensure that this project is a success and further contributes to Amgen's supply chain transformation goals are delineated in Chapter 5.

Chapter 5

Operational Improvements and Conclusion

This chapter delineates the operational implementation strategy for the proposed inventory management methodology at Amgen discussed in Chapters 3 and 4. A phased implementation plan is developed to ensure a seamless transition, starting with a pilot phase to quantify safety stock, and up to full scale deployment. In addition, warehouse operational improvements are addressed, highlighting the need for upgraded inspection systems, stringent supplier policies, and a shift to a first expiry first out (FEFO) system for dispensing raw materials, all designed to minimize scrap and align with the overarching goal of a more resilient supply chain.

5.1 Operational Implementation Strategy of Proposed Methodology

As discussed in Chapters 2 and 3, the organization has commenced systematic steps to refine inventory policies by applying segmentation techniques to reduce the months forward coverage (MFC) designation for each raw material. In contrast, the methodology proposed in Chapters 3 and 4 is a paradigm shift towards deriving safety stock quantities, and then using that to set the months forward coverage policy for a material, as opposed to the other way around that is currently being done at Amgen. This approach will not only help determine robust safety stock levels, but also ensure a more sustainable inventory management model.

To implement the proposed inventory management strategy effectively, a phased approach is essential. Each phase should leverage insights gained from the preceding phase in order to ensure a smooth transition. The following steps delineate suggested phases for implementation.

Phase 1: Pilot Safety Stock Quantification and MFC Determination

- Select pilot materials and determine safety stock levels by using the stochastic simulation model and overall framework proposed.
- Translate safety stock quantities into MFC and compare with exisiting policy.

Phase 2: Model Output Integration and MFC Optimization

- Utilize the model outputs to identify areas of improvement and MFC policy optimization across different material categories.
- Implement targeted reductions in MFC based on the model insights, ensuring that stock levels align with the actual demand patterns and reduce excess inventory, with minimized stock out risk.

Phase 3: Lead Time Management and Supply Planning

- Deploy the lead time forecasting model outputs to refine supply planning processes.
- Manage supplier lead times proactively by using forecasted times to mitigate risks associated with supply delays or disruptions.

Phase 4: Continuous Monitoring and Model Updates

- Monitor the performance of the proposed inventory policies against key performance indicators (KPIs) to gauge their effectiveness.
- Data science team to continuously train and update the machine learning models with updated data to improve forecast accuracy.

Phase 5: Training and Change Management

- Train key staff such as raw material planning team to familiarize them with the new methodology and results, emphasizing the thinking shift from MFC-to-quantities to quantities-MFC.
- Develop a change management plan to support the transition, addressing any concerns and reinforcing the benefits of the new approach.

Phase 6: Full Scale Deployment and Organizational Alignment

- Upon successful validation of the models and policies in the initial phases and pilots, proceed with a full scale deployment across all raw materials and other production stages of the supply chain.
- Ensure alignment across all key stakeholders such as the supply chain and raw material planning team and the warehouses.

Transitioning the organisation to a data-driven approach for raw material planning in phases will provide further insights into challenges that a full scale deployment could have. This will also ensure that all key stakeholders are on board and the solution is actually tailored to the risk tolerance level of Amgen, paving the way for a more resilient and efficient supply chain.

5.2 Warehouse Operational Improvements

In addition to the methodology devised for the raw material inventory management challenge, areas of operational improvement are identified below based on observations of operations in the warehouses.

Upgrade Inspection Systems in the Warehouse to Reduce Scrap: During a visit to one of Amgen's manufacturing plants, and discussing with the warehouse team, a key realization emerged: many of the contributions to the scrap from warehouses stems from material defects that are observed when the materials are dispatched to the manufacturing plant and labs. Another insight emerging from the visit is the inability to inspect every single item from all the suppliers due to infeasible manpower. Therefore, a recommendation is for the warehouses to implement automated vision inspection (AVI) or machine vision systems to help detect defects and minimize scrap and waste of raw materials. Konstantinidis et al. [51] utilized digital twins and machine vision to detect defects during the dairy manufacturing process. Implementing advanced technologies like machine vision can help drastically reduce stock out issues and scrap volumes in Amgen manufacturing plants, as these systems can detect anomalies more efficiently than the typical manual processes.

Impose Strict Policies for Suppliers: Another observation is that there are instances where suppliers deliver a batch of materials only to follow with another shipment, containing materials that have an earlier expiration date than those delivered previously. This potentially contributes to the scrap problem Amgen has, as the warehouses dispenses raw material to the manufacturing plants in a first in first out (FIFO) manner. Therefore it is recommended that a clause be included in supplier agreements, specifying minimum shelf life requirements upon receipt to ensure that received items have a consistent or longer shelf life than existing inventory. Also, Amgen should deploy a compliance tracking system to monitor supplier adherence to these policies.

First-Expiry-First-Out Warehouse Dispensing: The warehouse currently dispenses materials based on goods receipt date (GRD) which is a logical approach. However, due to some of the instances where recently received materials could have an earlier expiration date than older materials, the FIFO methodology of dispensing might not be the optimal strategy to reduce scrap. Therefore, implementing a first expiry first out (FEFO) system in the warehouse is recommended, to automatically dispense materials based on expiry dates rather than receipt dates.

5.3 Future Work

Multi-Echelon Inventory Optimization

This project focused purely on raw materials. However, the methodology developed can be applied to the drug Substance, drug product and finished drug product stages of production, which would enable better coordination of targets across the supply chain. Understanding stock levels, constraints, and variability at each point allows balancing risk across all stages instead of locally optimizing stages. This takes a systems view to support Amgen's "Every Patient, Every Time" policy while optimizing working capital.

Network Inventory Optimization

Effective inventory planning across Amgen's network of manufacturing plants and warehouses is important for ensuring operational efficiency, minimizing costs, and maintaining a reliable supply chain. Amgen could implement a centralized system to track inventory levels across all manufacturing plants and warehouses. This could also help foster coordination and communication across the manufacturing plants and warehouses to ensure efficient use of inventory. Amgen could also implement a redistribution strategy for transferring inventory between locations in response to demand fluctuations or supply chain disruptions, which would only be seamless with a centralized system.

5.4 Conclusion

This research makes significant contributions to the field of inventory management and supply chain optimization in the biotechnology industry. In an industry like biotech where the consequences of material unavailability are high, it is important to use data-driven approaches to ensure optimal inventory levels, while also deploying proper risk management strategies for risk mitigation. Operational efficiency is also key to ensure that there is no bullwhip effect and the entire supply chain runs smoothly.

By developing a comprehensive methodology that integrates machine learning, stochastic simulation, and multi-criteria segmentation, this work addresses the some of the limitations of existing approaches and provides a more dynamic, and risk-aware framework for safety stock determination. The integration of demand and lead time forecasting, Monte Carlo and disruption simulation framework, and raw material segmentation approach offer unique insights and practical solutions to the challenges faced by organizations in managing complex supply chains. The results and case studies presented demonstrate the potential impact of this work in driving cost savings, improving customer service levels, and enhancing overall supply chain resilience. A combination of data management, advanced data analytics, supplier relationship management, operational efficiency and effective communication will go a long way in reducing stock outs in companies like Amgen.

Appendix A

Tables

Model	Parameter	Values
LGBMRegressor	n_estimators	[50, 100, 200]
	max_depth	[3, 5, 7]
	num_leaves	[8, 32, 128]
	learning_rate	[0.01, 0.1, 0.2]
	subsample	[0.6, 0.8, 1.0]
	colsample_bytree	[0.6, 0.8, 1.0]
XGBRegressor	n_estimators	[50, 100, 200]
	max_depth	[3, 5, 7]
	learning_rate	[0.01, 0.1, 0.2]
	subsample	[0.6, 0.8, 1.0]
	colsample_bytree	[0.6, 0.8, 1.0]
RandomForestRegressor	n_estimators	[50, 100, 200, 300]
	max_depth	[None, 5, 10, 20, 30, 50]
	min_samples_split	[2, 5, 10]
	min_samples_leaf	[1, 2, 4, 6]
	max_features	['sqrt', 'log2']
Lasso	alpha	[0.1, 1.0, 10.0]
CatBoostRegressor	iterations	[100, 300, 500]
	learning_rate	[0.01, 0.05, 0.1]
	depth	[4, 6, 8]
	l2_leaf_reg	[1, 3, 5, 7]
	border_count	[32, 64, 128]

Table A.1: Hyperparameters of Lead Time Forecasting Machine Learning Models

Model	Hyperparameter	Values
LightGBM (`get_lgb_params`)		
	n_estimators	10, 50, 100
	max_depth	-1, 3, 5, 7
	num_leaves	31, 63, 127
	learning_rate	0.001, 0.01, 0.1
XGBoost (`get_xgb_params`)		
	n_estimators	50, 100, 200
	max_depth	3, 5, 7
	learning_rate	0.01, 0.1, 0.2
	subsample	0.6, 0.8, 1.0
	colsample_bytree	0.6, 0.8, 1.0
Random Forest (`get_rf_params`)		
	n_estimators	50, 100, 200, 300
	max_depth	None, 5, 10, 20, 30, 50
	min_samples_split	2, 5, 10
	min_samples_leaf	1, 2, 4, 6
	max_features	sqrt, log2
CatBoost (`get_catboost_params`)		
	iterations	50, 100, 300
	learning_rate	0.001, 0.01, 0.05, 0.1
	depth	4, 6, 8, 10
	l2_leaf_reg	1, 3, 5, 7
	border_count	32, 64, 128

Table A.2: Hyperparameters of Demand Forecasting Machine Learning Models

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