Optimization of Warehouse Operations and Transport Risk Mitigation for Disposable Bioreactor Bags to Support Launch of Amgen Singapore Manufacturing

by

Maxine Yang

B.S. Chemical and Biological Engineering, Massachusetts Institute of Technology, 2007

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

Master of Business Administration
and
Master of Science in Mechanical Engineering

In conjunction with the Leaders for Global Operations Program at the Massachusetts Institute of Technology

June 2015

Signature of Author _____ Signature redacted
Mechanical Engineering
MIT Sloan School of Management
May 8, 2015

Certified by _____ Signature redacted
Donald B. Rosenfield, Thesis Supervisor
Senior Lecturer, MIT Sloan School of Management

Certified by _____ Signature redacted
Daniel D. Frey, Thesis Supervisor
Professor of Mechanical Engineering

Accepted by _____ Signature redacted
David E. Hardt, Chairman, Committee on Graduate Students
Department of Mechanical Engineering, MIT

Accepted by _____ Signature redacted
Maura Herson, Director of MIT Sloan MBA Program
MIT Sloan School of Management

Optimization of Warehouse Operations and Transport Risk Mitigation for Disposable Bioreactor Bags to Support Launch of Amgen Singapore Manufacturing

by

Maxine Yang

Submitted to the MIT Sloan School of Management and the Department of Mechanical Engineering on May 8, 2015 in Partial Fulfillment of the Requirements for the Degrees of Master of Business Administration and Master of Science in Mechanical Engineering

Abstract

A strategic imperative for Amgen is to increase the number of patients that have access to the company's lifesaving medicines. As part of this goal, Amgen is launching a new manufacturing site in Singapore (ASM). Reliability of supply and quality control will be critical factors for successful ASM launch; therefore, this project will focus on two key objectives: optimization of raw material flow for the ASM warehouse, and transportation risk mitigation of disposable bioreactor bags.

Optimization of warehouse operations helps ensure the site can supply enough drug substance to meet the needs of patients worldwide. ASM has a warehouse that is 1/3 the size of a traditional biologics manufacturing warehouse, and is projected to reach capacity during commercial production, increasing risk for the site and incurring the cost of outsourcing storage. A Warehouse Capacity Model was developed using inventory management principles, and then used to identify operations strategies that provide the greatest improvement in warehouse utilization for ASM.

Transport risk mitigation for disposable bioreactor bags is critical to the manufacturing process, because ASM is using disposable technology throughout their drug manufacturing process. Even a pin-sized hole can lead to contamination and significant lost revenue. To reduce the risk to these bags during shipping, a twelve-member, cross-functional team was formed, consisting of experts at Amgen from seven different functional groups, including materials science and supply chain, to partner with the supplier to establish a transportation qualification plan for the 2000L bioreactor bag. Transport risk mitigation of bioreactor bags also reduces the required amount of storage, since fewer bags will need to be stored as safety stock. The transport qualification of 2000L bags was successfully executed, and the process was documented to guide future transportation qualification plans for disposables.

The key recommendations are that in the short-term, ASM should hold materials with suppliers with warehouses in Singapore, increase frequency of delivery of materials, and utilize random storage location assignment. In the longer term, ASM should utilize storage from suppliers and Third Party Logistics Providers (3PL). For future warehouses, the Warehouse Capacity Model should be used in the design phase to give the team sufficient time to implement recommendations. For future transportation qualification plans for disposables, a pressure decay method is recommended for more robust testing of bag integrity. In addition, creation of a "library" of defects is recommended to improve visual inspections.

Thesis Supervisor: Daniel D. Frey
Professor of Mechanical Engineering

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

This page intentionally left blank.

Acknowledgments

First and foremost, I would like express my gratitude to Amgen for sponsoring my LGO internship. Amgen's Supply Chain organization provided me with a rich learning experience in an international context. My sincerest thanks go to my manager Jared Byrne for his instrumental effort in coaching me and helping me grow both professionally and personally. I also wanted to thank Kimball Hall for sponsoring my internship, and Dave Stadolnik for managing the internship experience and ensuring the entire process went smoothly.

The work in this thesis is the result of collaboration between many teams within Amgen. I would like to thank my manager, Jared Byrne, for his instrumental effort in coordinating the various individuals and providing me with valuable resources. A great number of individuals within Amgen contributed to this thesis, and in particular I would like to thank Victor Matos, Kris Lee, and Matt Shields from the Amgen Singapore Manufacturing team for supervising me and providing a solid foundation for my analytical work to build upon. In addition, for transportation qualification of disposables, I'd like to thank the following individuals: Jan Meier for helping me lead the project, Sally Kline and Weibing Ding for their technical expertise on materials, Takeshi Nishiura and Mike Vandiver for their expertise in process engineering, Chris Fong and Kelly Van Arsdale for their expertise on transportation qualification, Ron Etemadi for supplier quality, and Dave Cady and Tim Bustillos for global strategic sourcing.

I would also like to acknowledge the Leaders for Global Operations program for its support of this work. Furthermore, the successful completion of this thesis would not be possible without the critical guidance from my MIT faculty advisors Dr. Donald B. Rosenfield and Dr. Daniel D. Frey. I am grateful for their insights that shaped the development of my thesis, and I appreciate their time and patience guiding me throughout this project.

I would also like to thank my fellow LGO classmates. I am just amazed at the diversity of backgrounds and the talent of the students in my program, and at the same time how down-to-earth and collaborative they are. It has been an incredible journey, and in just two years, they feel like family.

Lastly, I would like to thank my family for all of their tremendous support: my father, who dedicated his life to designing medical devices, inspired me to pursue a career to improve the health of others; my mother, who is always there to support me, no matter the obstacle; and my younger brother, who inspires me to be a good role model everyday. Together, their unwavering faith in me has helped me overcome numerous challenges, and I am forever thankful to have them in my life.

This page intentionally left blank

Table of Contents

List of Figures

List of Tables

1 Company Background

1.1 Introduction to Biotechnology

Biotechnology is the use of biology to develop or make useful products. The term was coined in 1919 by Hungarian engineer Karoly Ereky. Ereky's vision has now been realized by thousands of companies and research institutions ("What Is Biotechnology?"). The growing list of biotechnology products includes medicines, medical devices, and diagnostics, as well as more-resilient crops, biofuels, biomaterials, and pollution controls. Amgen was one of the first companies to recognize the potential of biotechnology specifically in the development of medicines. Today's biologic medicines have made a significant difference to the lives of patients with serious illnesses, including cancer, blood conditions, auto-immune disorders such as rheumatoid arthritis and psoriasis, and neurological disorders like multiple sclerosis.

This chapter will provide an overview of the company, followed by a review of the expansion to Singapore, and conclude with the company's organizational structure.

1.2 Company Background

Founded in 1980 as Applied Molecular Genetics, Amgen focused on the development of biotechnology medicines, large molecules that are similar or identical to the proteins and other complex substances in the body, and are used for treating, preventing, or curing disease. Backed by several million US dollars in venture capital funding, and led by a former Vice President at Abbott, the company received approval for the first recombinant human erythropoietin product, Epogen, for the treatment of anemia associated with chronic kidney failure.

Amgen has become a leader in the discovery, development, and delivery of human therapeutics for patients suffering from serious illnesses. The company is now the largest independent biotechnology company in the world, selling to millions of patients in the fight against cancer, kidney disease, rheumatoid arthritis, bone disease and other serious illnesses. The company now markets 12 different products in over 75 countries, with $18.7 billion annual revenue (2013).

Amgen's products currently on the market include: Aranesp® (darbepoetin alfa), Enbrel® (etanercept), EPOGEN® (epoetin alfa), Kyprolis® (carfilzomib), Neulasta® (pegfilgrastim), NEUPOGEN® (filgrastim), NEXAVAR® (sorafenib), Nplate® (romiplostim), Prolia® (denosumab), Sensipar® / Mimpara® (cinacalcet), Vectibix® (panitumumab) , XGEVA® (denosumab), and Blincyto™ (blinatumomab).

1.3 Amgen Singapore Manufacturing

A strategic imperative for Amgen is to increase the number of patients that have access to the company's lifesaving medicines. As part of this goal, Amgen is launching a new manufacturing site in Singapore (ASM). Over the next several years, Amgen anticipates investing $200 million to build an innovative new facility (Palmer 2015), which will initially focus on expanding Amgen's manufacturing capability for monoclonal antibodies[1]. In addition to greater access to the Asian market, Singapore provides the additional benefits of having a rich talent pool and a friendly business environment.

Amgen's planned manufacturing site in Singapore represents great potential for the company, due to use of single-use, disposable bioreactor technology across the entire manufacturing process, a first for the industry. The use of disposable technology at ASM embodies the company's mission of serving patients, and its history of pioneering breakthrough technology. The opening of the company's first manufacturing site in Asia will generate the potential of serving more patients, and being the first company in the biotechnology industry to develop and use disposable technology is in line with the company's pioneering spirit. In fact, many global launches of new manufacturing sites for Amgen are slotted to utilize the disposable technology.

With this enthusiasm, however, comes high expectations. There is pressure from senior leadership to reduce cost and risk; many teams are now developing ways to address this challenge. My project objectives are in line with this goal: The ASM warehouse is only 1/3 that of a traditional biologic manufacturing warehouse and is projected to reach maximum capacity during commercial production, so improving efficiency of warehouse operations will be important. Raw material flow optimization will increase warehouse operational efficiency and minimize the cost of storing unnecessary inventory, while reducing the risk of stock-outs. Additionally, given the company is utilizing the disposable bioreactor technology across ASM's entire drug manufacturing process, maintaining quality of the disposable bags will be required to ensure drug quality. The transport validation plan will reduce the risk of damage to high-cost disposable materials during shipping. A big part of Amgen's company mission is to reliably deliver high-quality medicines to patients who need them, so reliability of supply and quality control will be critical factors for successful ASM launch.

[1] Monoclonal antibodies are mono-specific antibodies that are made by identical immune cells that are all clones of a unique parent cell. They can be designed to specifically bind to any substance, making them ideal candidates for medicine, especially in cancer treatments, where they can be engineered to attach to specific defects in cancer cells ("Monoclonal Antibody").

1.4 Organizational Structure

Amgen's organizational structure is grouped by functional activities, which facilitates strong innovation within the team. Key functions are led by Executive Vice Presidents (EVP), who report directly to the CEO, Bob Bradway. The five EVP's at Amgen are Madhu Balachandran for Operations, Sean Harper for R&D, Anthony Hooper for Global Commercial Operations, David Meline for Finance, and Brian McNamee for the Amgen Full Potential Initiative. In addition, there are 17 Senior Vice Presidents (SVP), spanning functions from Business Development to Manufacturing. The SVP's for which the content in this thesis is most relevant include Alison Moore, SVP of Process Development, Esteban Santos, SVP of Manufacturing, and Martin VanTrieste, SVP of Quality.

Kimball Hall, VP of manufacturing at Amgen, is responsible for launching ASM, with her team of directors, senior managers, and other subject matter experts, spanning functions from Quality to Supply Chain. My key deliverables are to optimize the raw material flow for warehouse operations at ASM and to develop transport validation of critical disposable materials to ensure they arrive at ASM undamaged. Improving warehouse efficiency and mitigating risk to disposable materials is directly aligned with Kimball Hall's deliverable of launching ASM. I am an individual contributor on the flow optimization, and my deliverable is outlining the amounts for each raw material with just-in-time inventory replenishment, without stock-outs. For transport validation, I am a team leader, and I led a cross-functional team to create a transportation risk mitigation plan for disposable materials. I directly reported to Jared Byrne, who reported to Kimball for project management for ASM. For day-to-day activities, I worked with Kris Lee, Supply Chain Manager, who is also in Kimball's organization.

Amgen has undergone some recent organizational changes. First, Jared Byrne now reports to Alison Moore in Process Development, although he has remained my manager through the completion of my project for ASM. Second, Kris Lee has since left Amgen, so I worked with her manager, Matt Shields, plant manager of ASM, during the interim period before her replacement, Victor Matos, was identified. My transport validation work remained unaffected; I worked with Jan Meier, Director of Raw Materials and Devices.

1.5 Thesis Outline

This thesis is organized into seven chapters. The content of each chapter is summarized below.

- Chapter One provides an overview of Amgen and the biotechnology industry. Relevant background information is provided relating to Amgen's products, mission and organizational structure.

- Chapter Two describes the context of the problem faced by the organization, the objective of the project and how the research was conducted.
- Chapter Three gives an overview of the literature that was consulted to formulate the two research areas into a cohesive structure.
- Chapter Four details the Warehouse Capacity Model, reviewing model development and functionality, then discusses the results of ASM warehouse capacity analysis using the model, including operations strategies to improve utilization, and maximizing the benefit of warehouse models in the future.
- Chapter Five describes the transportation risk mitigation plan for disposable materials, including development, implementation, results and future recommendations.
- Chapter Six closes the thesis with key takeaways and potential future work in each research area.

2 Introduction

The content in this thesis outlines the results of a six-month internship with Amgen Inc. from February 2014 to August 2014. The internship was championed by the Amgen Singapore Manufacturing team (ASM) with a task to support warehouse initiation activities for the launch of Amgen Singapore Manufacturing. Two issues were identified:

1) ASM warehouse will hit capacity in the next few years, increasing risk and cost.
2) No process exists to ensure the quality of disposable, single-use bioreactor bags is maintained in transit, from origin to destination (typically from Eastern U.S. to Singapore). One defective bag could lead contamination of an entire batch, resulting in millions of dollars of lost revenue.

During the six-month period, the internship was based at Amgen's company headquarters in Thousand Oaks, California, but involved members of the ASM team, most of which was located at the Thousand Oaks site at the time of the internship, and transitioning to Singapore for the opening of the site in November of 2014. For the optimization of materials in the warehouse, I was an individual contributor on the ASM team, and my deliverable was to outline the placement and amounts for materials with just-in-time inventory replenishment, without stock-outs. For the single-use bioreactor bags, I created and led a cross-functional team to establish a transportation qualification plan to mitigate transport-related damage. Twelve members from the following departments contributed to this effort: Raw Materials and Devices, Materials Science, Packaging Engineering, Process, Transportation, Supplier Quality Management, and Global Strategic Sourcing.

2.1 Problem Statement

Amgen has embarked on an effort to increase the impact that its products make in people's lives. To meet this goal, the company is launching a new manufacturing site in Singapore. While Amgen has experience in startup of new manufacturing plants, ASM poses some unique challenges for the organization, including ASM's small footprint and warehouse, and the use of single-use technology across the entire drug manufacturing process. Challenges faced by ASM can be summarized as follows:

1. The ASM warehouse was originally designed to support full production and hold one month safety stock, but the Warehouse Capacity Model (explained in detail in Chapter 4) shows the warehouse can only hold five manufactured drug batches[2] worth of cycle stock, and no safety

[2] Amgen manufacturing is measured in manufactured drug "batches," not to be confused with a supply chain "batch," which is the amount of raw material in each order. To avoid confusion, a "batch" always refers to a batch of manufactured drug, while "order quantity" refers to the amount of raw material in each order.

stock[3] (Figure 1). (Note: cycle stock refers to the stock on-hand to support production, while safety stock, also called "forward coverage," is the stock used as buffer to mitigate stock-outs.)

2. Many changes since the development of the ASM site contributed to the increase in capacity utilization: increases in quantities of items in Bill of Materials (Figure 2), higher levels of manufacturing in the new long-range plan for ASM (Figure 3), and additional required storage for ASM site operations (Table 1).

3. By 2018, the warehouse will run out of capacity to meet production targets, as set by the ASM long-range plan. The warehouse will need to utilize Third Party Logistics Provider (3PL) or suppliers (Figure 5) for additional capacity.

4. Transport qualification is currently not completed for high-risk materials, and should be completed for risk mitigation.

The ASM warehouse is projected to fall short by 2017. To reduce cost and risk for the site, Amgen needs to implement operations strategies to reduce warehouse capacity utilization. However, even with these strategies in place, the ASM warehouse will reach capacity by 2018, and need to hold additional storage either with suppliers or at a 3PL in order to meet target production levels. Additionally, since Amgen is the sole patent owner and maker of the life-saving drug that will be produced at ASM, the company generally stores a higher amount of safety stock than other industries to ensure that they always support "every patient, every time." A significant portion of required storage is taken by safety stock, so transport risk mitigation of high-risk not only reduces risk for the site, but also can reduce required amount of storage as well (Figure 4).

[3] To illustrate, if Amgen manufactures one drug batch per week, 52 weeks per year, and Amgen orders material every 12 weeks, the order quantity will be the amount of raw material to make 12 batches, with six drug batches on average stored in the warehouse (half the order quantity). In this case, ASM won't be able to store all of the cycle stock, because ASM can only hold raw material for five manufactured drug batches in the warehouse at a time.

Figure 1. Warehouse capacity will fall short by 2017

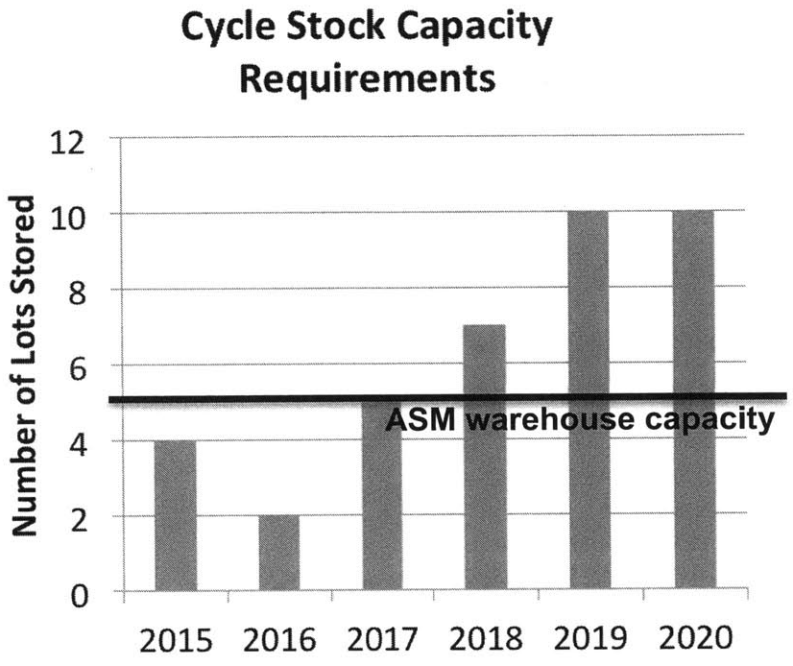


Figure 2. Changes in bill of materials quantities contributed to increase in warehouse utilization

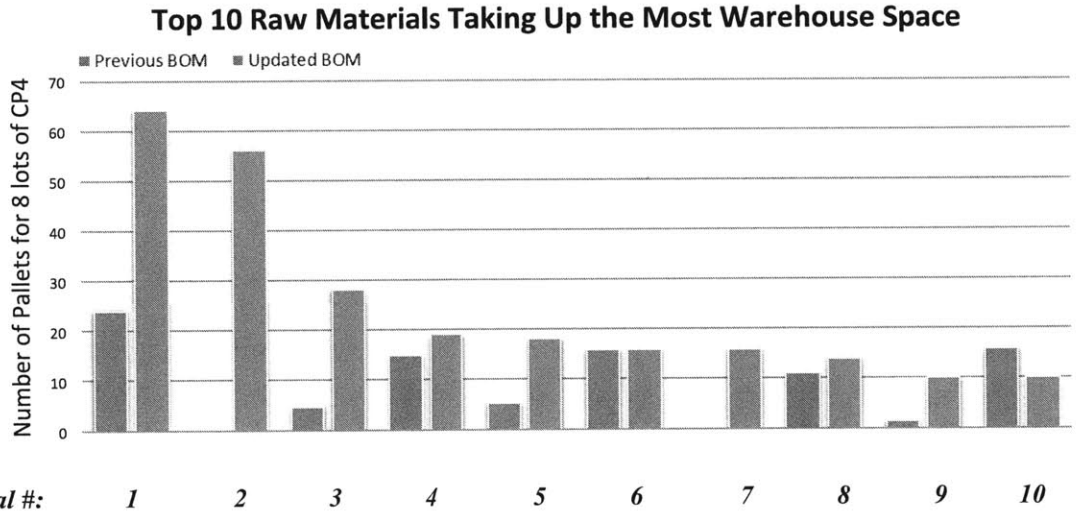


Figure 3. Manufacturing levels in new long range plan (2014) is higher than 2013

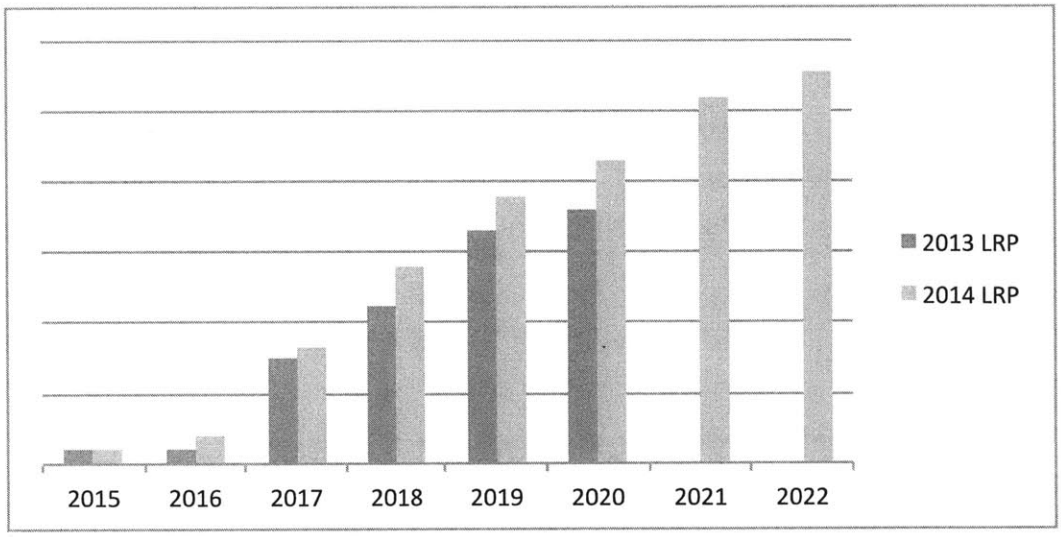
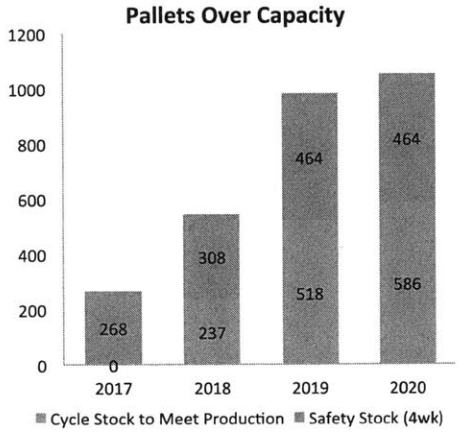


Table 1. Additional storage required for ASM site operations

Main storage (Controlled Room Temperature, CRT)	564 pallets available
Additional storage required for site operations • Reject cage: 15 • Quality testing: 10 • Containers for drug substance: 25 • Consumables: 50	100 pallets required
Remaining storage	464 pallets remaining

Figure 4. ASM will reach capacity by 2018, even with operations strategies[4]



[4] *Pallet projections take into account recommended operations strategies, covered in Chapter 5.*

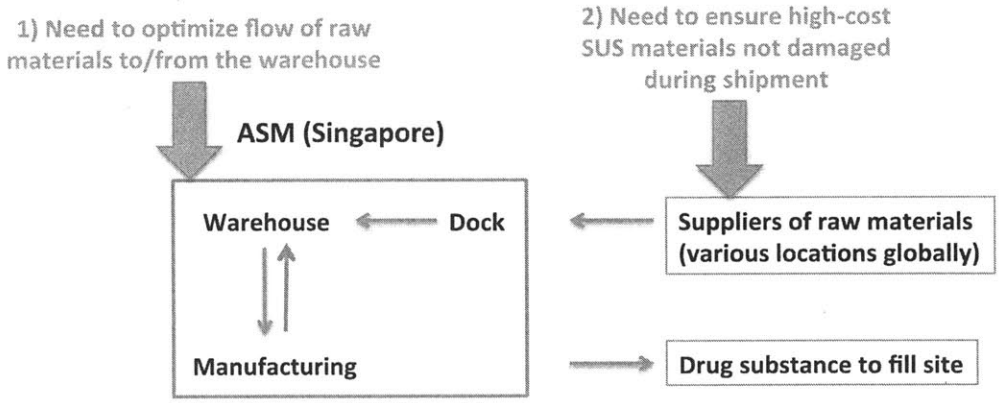
2.2 Project Objectives

This thesis will explore the risks and challenges associated with the launch of ASM, specifically in the area of ensuring reliable delivery and supply, by achieving the following objectives below. The results of the thesis will provide valuable insight into methods that can be used to improve the development of other Amgen warehouses in the future. Specifically, I will address the following:

1. Develop raw material flow strategy for the warehouse to ensure warehouse runs at maximum efficiency, minimizing costs such as labor, capital and storage
    a. Gather information about ASM warehouse operations and utilize inventory management principles to develop the Warehouse Capacity Model
    b. From model, identify operations strategies that would be most effective in improving utilization, for execution by the ASM team
2. Establish qualification for single-use, disposable bioreactor bags, to mitigate risk of damage during transport
    a. Create and lead cross-functional team to establish transport qualification plan for single-use, disposable bioreactor bags
    b. Provide recommended guidelines for future transport qualification plans for single-use, disposable materials

Figure 5 provides a schematic of the two research areas and their relation to ensuring reliable delivery and supply of drug substance from ASM. Raw materials are sent from supplier to ASM, and drug substance is delivered from ASM to fill site. Transport qualification is important to ensure quality of materials from supplier remain undamaged while in transport. Raw material flow optimization of ASM warehouse helps ensure ASM can meet target production of drug substance, to ship to fill site for final packaging into injectable devices, such as vials and syringes.

Figure 5. Supply of raw materials to ASM, and drug substance from ASM to fill site



2.3 Research Methodology

Due to the nature of the project and differing target goals of the overall improvement of operations for launch of ASM, different methodologies were used for the respective research areas. Each approach is outlined below:

1. ASM Warehouse Raw Material Flow Optimization

Warehouse Capacity Model

- Model development using inventory management principles: details incorporation of safety stock, cycle stock, and process stock into inventory calculations, collection of data for the model, as well as additional accommodations for site operations
- Model elements and functionality: provides a step-by-step user guide for using the model
- Process for using the model: discusses how the model can be used to guide warehouse strategy

Results and Recommendations

- Assessment of ASM warehouse capacity utilization over the next several years: provides a projection of warehouse utilization based on annual production targets for ASM
- Operations strategies to improve capacity utilization, and long-term options for ASM: reviews the operations strategies with the greatest impact on capacity utilization, as guided by the Warehouse Capacity Model
- Future directions: maximizing the benefit of Warehouse Capacity Models. This section contains an analysis of an additional warehouse, demonstrating the improved benefit of a Warehouse Capacity Model when it is applied earlier in the design phase of the warehouse.

2. Transportation Qualification of Single-use, Disposable Bioreactor Bags

Transportation Qualification Plan

- Selection criteria: identifying high-risk materials for transport qualification. This section provides criteria for assessing the level of shipping risk to disposables materials
- Transport qualification steps taken for single-use, disposable bioreactor bags: provides recommended steps for creating a robust transportation qualification plan, from defining critical to quality attributes, to performing final qualification studies

Results and Recommendations

Recommended guidelines for transportation qualification of disposable technology: there were several key learnings from this work that can guide future development of transportation qualification plans, particularly in the areas of bag integrity testing and visual inspections

3 Literature Review

Prior to developing the ASM warehouse raw material flow optimization and the transport qualification of single-use disposables, a significant amount of effort was expended to research the existing approaches applicable to each. For the raw material flow optimization, the model described in MIT Leaders for Global Operations program thesis, Raw Material Inventory Planning in a Serial System with Warehouse Capacity (Choi 2014) served as the starting point for the inventory management model. Modifications were then made to meet the needs of the ASM site at the time of this project. Further analysis was performed to determine the type of storage assignment that would best fit the needs of ASM. Initial findings in literature on warehouse performance (Gu, Goetschalckx, and McGinnis 2010) were used for this analysis. For transport qualification, relevant test standards were reviewed to develop the transport qualification plan for ASM's single-use, disposable bioreactor bag.

For both topics, there is a substantial amount of literature with a number of differing approaches. Each approach has limitations as to why one approach may be more suitable over another. In the following sections, a review of relevant aspects to each topic will be covered.

3.1 Inventory Management Principles Used for Raw Material Flow Optimization

Given the approaching deadline of ASM launch in November of 2014, this thesis focused on inventory management principles of highest urgency and value to the site. The other inventory management principles found in Choi's thesis are covered briefly, but will not be emphasized in this project.

Inventory policy refers to type of inventory replenishment model. In periodic review, inventory level is checked periodically and an order is placed at that time to meet the expected demand until the next order. In continuous review, inventory is continuously monitored and orders are placed with freedom of time. Periodic review requires less staff support for implementation, but continuous review typically leads to lower safety stock levels. ASM will initially implement periodic review, due to staffing constraints, but has the IT systems in place for tracking inventory continuously, so they have the capabilities for implementing continuous review in the future, if desired.

Process stock refers to the inventory that is currently being processed. Process stock can be calculated by D*L, where D is the demand and L is the lead time. At ASM, the process stock in the warehouse consists of inventory currently undergoing quality testing, called "test and release" at Amgen.

Cycle stock is the amount of material needed in the warehouse to meet target production. The amount required was calculated using numbers from Amgen's annual production plan, which sets the

amount of manufacturing batches of drug substance to be made per year for the manufacturing site. Given an order frequency and the desired production level, the order size can be calculated (also referred to as "lot sizing," which was covered in Choi 2014). On average, there will be half the order size in inventory; this is the average amount of cycle stock in the warehouse.

Safety stock, also referred to at Amgen as "forward coverage," is the inventory to cover for the variability in demand and lead time. The amount of safety stock can be calculated by the equation below, which takes into account variation in demand and lead time (Silver, Pyke, and Peterson 1998).

$$\text{SS} = Z * \sqrt{Average\ Lead\ Time * STD\ Demand^2 + Average\ Demand^2 * STD\ Lead\ Time^2}$$

Where Z = normsinv(service level), which returns the inverse of the standard normal cumulative distribution for a specified service level.

The amount of required safety stock can be calculated using service level. One way to determine service level is to compare the overage and underage cost with the Newsvendor, or the single-period model. A ballpark estimate for appropriate service level for biologics manufacturing in general (i.e. not specific to Amgen) can be calculated by applying the Newsvendor model to the estimated cost of production and sale price of a drug taken from Snow, Wheelwright, and Wagonfeld 2006. The Newsvendor model uses the ratio of the overage and underage cost to determine the appropriate service level. A sample calculation is provided below.

Service level calculation, using industry figures only (Snow, et al. 2006)

Underage cost calculation:

Given the sale price of $2000 per 0.375g single dose of the drug, the drug brings a revenue of $5.3 million per kilogram of drug.

Overage cost calculation:

Average output per plant is 1170 kg.

200 kiloliters * 15 batches/year * 0.75g/L * 0.80 useful batches * 65% yield = 1170 kilograms

Cost of plant is $600 million

Assuming a 10-year life for the plant, this means each plant can produce 11,700 kg before it is retired. Therefore, the overage cost is %600 million/11700 kg = $51280/kg

Applying the Newsvendor model equation yields a service level of 99.05%

$5.3M/(5.3M+51280) = 99.05%

The total amount of inventory stored in the warehouse at any given time can be calculated by the sum of the cycle stock and the safety stock. This was used to calculate capacity utilization for the ASM warehouse.

Other areas of inventory management covered by Choi 2014 included *ABC classification, commonality,* and *vendor managed inventory* in his thesis. The *ABC classification* approach was not recommended by subject matter experts at Amgen, because classification based on monetary value alone does not meet the needs for the raw materials stored at ASM. For example, sodium chloride is a low-value item, but operations managers often prefer to store extra, because it takes up a relatively small amount of volume, and they prefer to have one round of quality testing for a larger order size to save on time. Choi's recommendations on *commonality* and *vendor managed inventory* were appropriate for ASM, so they were implemented into the Warehouse Capacity Model.

3.2 Storage Assignment Methods for Material Warehouses

The storage location assignment problem (SLAP) is to assign incoming products to storage locations in storage departments/zones in order to reduce material handling cost and improve space utilization (Gu, Goetschalckx, and McGinnis 2007). Different warehouse departments might use different SLAP policies depending on the department-specific SKU profiles and storage technology. The selection of storage strategy affects warehouse design and has long-term effects.

Gu, Goetschalckx, and McGinnis 2007 describes the formal definition of SLAP:

Given

1) the storage area, including its physical configuration and storage layout,
2) information on storage locations, including their availability, physical dimensions, and location,
3) information on the set of items to be stored, including their physical dimensions, demand, quantity, arrival, and departure times,

Determine the physical location where arriving items will be stored.

Subject to performance criteria and constraints such as storage capacity and efficiency, picker capacity and efficiency, response time, and compatibility between products and storage. The ASM

warehouse is space-constrained, and the drug manufacturing process at ASM is a batch process with a known, deterministic demand, set by the annual production schedule for the site, so a space-efficient storage strategy with operationally simple implementation is ideal.

There are many warehouse storage strategies discussed in the literature, the most popular of which are random, dedicated, and class-based, each with its advantages and disadvantages. Random storage location assignment assigns incoming shipments to any open storage location. The key benefits of this method over other methods are its straightforward implementation and that it is more space-efficient, which is suitable for smaller warehouses (Gu, Goetschalckx, and McGinnis 2007). However, random location assignment may require more effort to accurately track the inventory. Dedicated storage assigns each material to a specific location in the warehouse. Significant reductions in travel time are obtainable from dedicated storage compared with random storage (Gu, Goetschalckx, and McGinnis 2010). However, dedicated storage requires much more warehouse space for implementation, given that each storage location can only hold one specific material. Class-based storage provides an alternative that is in between and has the benefits of both dedicated and random storage. In class-based storage, additional decisions are to determine the number of classes and to assign products to classes. Class-based storage with relatively few classes has been shown to yield travel time reductions that are close to those obtained by dedicated storage (Gu, Goetschalckx, and McGinnis 2007). The implementation of class-based storage (i.e., the number of classes, the assignment of products to classes, and the storage locations for each class) has significant impact on the required storage space and the material handling cost in a warehouse. One problem with class-based storage can be illustrated with the following situation: given a storage area is divided into separate zones and each incoming shipment must be stored within a specified zone, it might happen that the assigned zone does not have sufficient space to accommodate the incoming shipment, but another zone does. In this case, class-based storage is still not as space-efficient as random storage. Gu, Goetschalckx, and McGinnis 2007 describes another complexity with class-based storage: when the storage area is divided into separate zones and any incoming shipment must be stored within a single zone, it might happen that none of the zones has sufficient space to accommodate an incoming shipment. In such cases, it is advisable to free some space in a certain zone to accommodate the incoming shipment by shifting some stored products in that zone to other zones. This adds operational complexity, which must be weighed against the travel-time savings of this type of storage assignment. A strong case can be made that additional research is needed, especially to clarify the conditions under which the storage policy does or does not have a significant impact on capacity or travel time.

3.3 Relevant Test Standards for Transportation Qualification

The purpose of transport qualification is to test containers to determine their ability to protect the functionality of bioreactor bags during worldwide distribution. As such, several testing standards are relevant (Table 2).

Table 2. List of relevant testing standards for transport qualification

	Document Name	Document Number
1	Leak Rate	DIN EN 1330-08
2	Atmospheric Conditioning	ASTM D 4332
3	Compression Test	ASTM D 642
4	Fixed Displacement Vibration Test	ASTM D 999
5	Drop Test	ISTA 2A/ASTM D 5276
6	Random Vibration Test	ASTM D 4728

The most critical testing standard is DIN EN 1330-08, which defines the leak test for the bioreactor bag. According to DIN EN 1330-08, a Leak Rate is defined as a pV-throughput [in Pa mN/s] of a specific fluid, which passes through a leak under specific conditions.

$$q_L = \frac{\Delta(p \cdot V)}{\Delta t}$$

where p is pressure, V is volume, t is time, and q_L is leak rate

A test specimen can only be qualified in comparison with a maximum acceptable leak rate $q_{L,acc.} > 0$ because according to DIN EN 1779, it is not allowed to specify a leak rate of $q_{L,acc.} = 0$.

The actual leak rate q_L determines if the test is:

passed $q_L < q_{L,acc.}$ (leak-tight) or failed $q_L \geq q_{L,acc.}$ (leak-tight)

$$q_L = \frac{d(p \cdot V)}{dt} = V \cdot \frac{dp}{dt} + p \cdot \frac{dV}{dt}$$

Assuming volume is constant,

$$\frac{dV}{dt} = 0$$

$$q_L = V \cdot \frac{dp}{dt} \approx V \cdot \frac{\Delta p}{\Delta t}$$

The acceptable leak rate has to be chosen for the individual application. Rough values for air leak ranges are given in Table 3 ("Leak Test Methods, Reference Leak Rates" 2015). For pharmaceutical applications, an integrity test is leak test where the leak rates are generally comparable to bacteria tightness and are correlated to a microbial challenge.

Table 3. Rough values of acceptable leak rates for various applications

Specifications	**Acceptable leak rate, with air [mbar*l/s]**	**Acceptable leak rate, with air [ml/min]**
Water tight	$< 10^{-2}$	< 0,6
Oil tight	$< 10^{-3}$	< 0,06
Gasoline tight	$< 10^{-5}$	< 0,0006
Steam tight	$< 10^{-3}$	< 0,06
Gas tight	$< 10^{-6}$	$< 6*10^{-5}$
Bacteria tight	$< 10^{-4}$	< 0,006
Virus tight	$< 10^{-7}$	$< 6*10^{-6}$
Absolutely (technically) tight	$< 10^{-10}$	$6*10^{-9}$

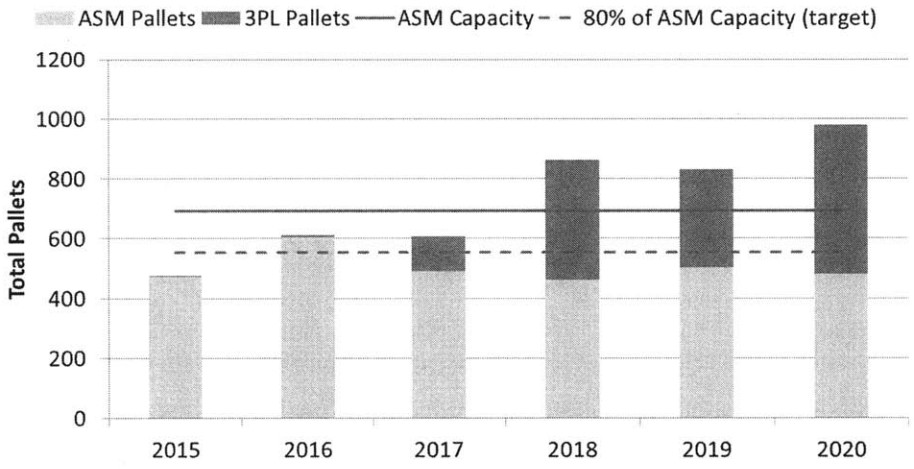
Testing standards 2-6 (Table 2) are relatively straightforward, and therefore are not reviewed in this chapter. Their application to disposable bioreactor bags is discussed further in Chapter 5.

4 ASM Warehouse Capacity Model

4.1 Previous risk assessment for ASM warehouse capacity utilization

Prior to this project, an initial assessment of ASM warehouse capacity was performed by Jason Choi (Choi 2014). In his thesis, Jason Choi estimated that ASM warehouse would exceed 100% capacity by 2018, and suggested utilizing a Third Party Logistics Provider (3PL) in 2017, to stay under his recommended level of 80% capacity utilization (Figure 6). Given the many changes to ASM between Jason Choi's work and the timing of this project, significant increases to capacity utilization are expected (Chapter 2).

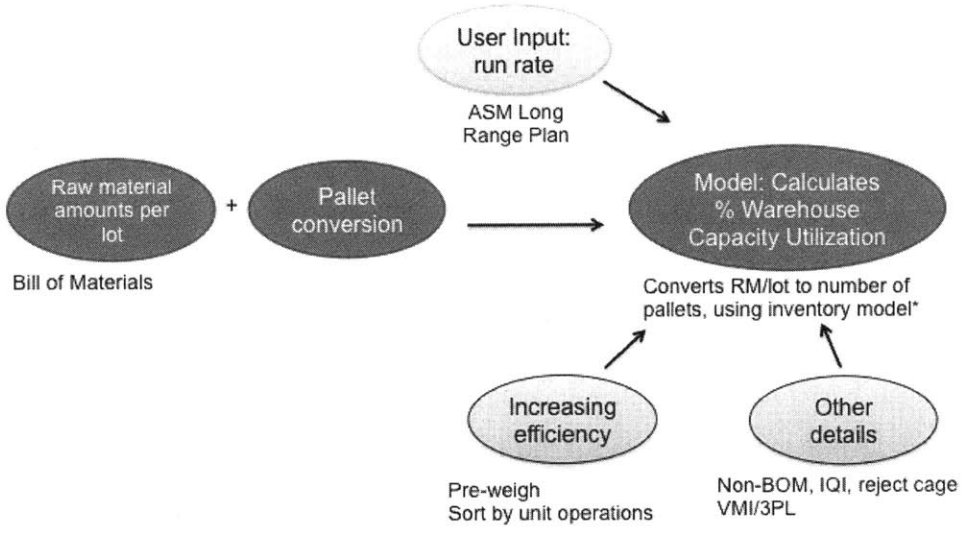
Figure 6. Jason Choi's estimate of ASM's capacity utilization



4.2 Model Development Using Inventory Management Principles

To initiate the development of the Warehouse Capacity Model, the first step was to identify the inventory management principles to calculate percent utilization. Figure 7 summarizes all model elements in a schematic diagram. This project focused on using a modified average inventory calculation to fit Amgen's production needs. Jason Choi's model was used as a starting point (Choi 2014) and modifications were made according to the needs of ASM. A significant amount of data was collected to improve model accuracy: production forecast for ASM, Bill of Materials to make the drug substance, pallet conversion numbers for each material, and test and release time. Additional storage accommodations were also incorporated for site operations, which occupied additional space in the warehouse.

Figure 7. Schematic of all model elements



4.2.1 Average Inventory Calculation

The average inventory was calculated from the sum of cycle stock, safety stock and process stock (which consists of raw material testing and release). Note that seasonal stock does not apply here, because Amgen sets a target production level for each year. The total capacity utilization of the ASM warehouse was determined by dividing the average inventory by the total available storage.

$$Cycle\ Stock + Safety\ Stock + Process\ Stock = Average\ Inventory$$

$$\boldsymbol{Percent\ Utilization = \frac{Average\ Inventory}{Available\ Storage} \cdot 100}$$

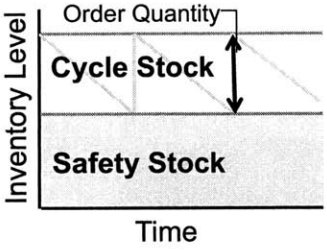
There are six storage areas in the ASM warehouse (Table 3), so this calculation was repeated to calculate the percent utilization for each storage area. The calculation of cycle stock, safety stock, and process stock are detailed below.

Table 4. Storage areas in the ASM warehouse

Storage Condition Type	Description
Controlled Room Temp (CRT)	Largest storage area, for disposables and many chemicals
2 - 8C	Cell culture media
CRT Acid	Acids, such as some alcohols
CRT Base	Bases, such as sodium hydroxide
CRT Flammable	Flammables, such as some resins
2-8C Flammables cabinet[5]	Certain flammables required to be stored at 2-8C

[5] Measured in liters of liquid stored

Figure 8. Cycle stock and safety stock diagram



Cycle Stock Calculation

First, the average cycle stock, in number of manufacturing batches, was calculated. On average, there will be half the order size in inventory; this is the average amount of cycle stock in the warehouse.

$$Average\ Cycle\ Stock = \frac{Order\ Size}{2}$$

The order size can be calculated from a given order frequency and desired production level.

$$\frac{Production\ Rate}{Order\ Frequency} = Order\ Size$$

Order frequency, the number of orders per year, is constrained due to required quality testing per FDA requirements. Each incoming shipment is required to undergo FDA testing; therefore, a lower order frequency requires a higher level of staffing to support quality testing. The order frequency was estimated from the number of weeks between orders that could be supported by the current ASM staffing level.

Desired production level is guided by Amgen's annual production plan, which sets the amount of manufacturing batches of drug substance to be made per year for the manufacturing site. From the annual plan, the plant manager will determine the "run rate," which, at Amgen, is defined as the number of weeks between batches of drug substance manufactured. The reciprocal of the Amgen run rate multiplied by 52 weeks yields the average *annual production rate*, or the number of batches per year.

Second, the number of manufacturing batches was converted to the number of pallets stored in the warehouse, using Y_k, the pallet conversion number.

$$Pallets\ Stored = Average\ Cycle\ Stock \cdot \sum_{k=1}^{n} X_k Y_k$$

where X_k is units of material k required per manufacturing batch, and Y_k is the pallet conversion number, which is the number of units of material k that fit on a pallet.

Safety Stock Calculation

For an estimated lead time of 4 weeks, lead time STD +/- 10% = 0.48 weeks, demand of 40 batches per year, and a demand STD +/- 10% = 4 batches, and applying the safety stock equation below, the estimated amount of safety stock required would be four weeks.

$$SS = Z * \sqrt{Average\ Lead\ Time * STD\ Demand^2 + Average\ Demand^2 * STD\ Lead\ Time^2}$$

Since Amgen is the sole patent owner and maker of the life-saving drug that will be produced at ASM, safety stock is often targeted to cover the most that could be needed and does not use the typical probabilistic approaches (i.e. setting a service level less than 100% is currently not seen as a responsible approach within the industry). Therefore, in the model, safety stock was treated as a variable that could be input by the ASM operations manager, in the form of number of weeks of forward coverage in addition to the cycle stock currently stored in the warehouse. This number was then converted to an equivalent number of pallets of storage.

Process Stock ("Testing and Release of Materials")

The contents of each incoming raw material shipment to the ASM warehouse need to undergo quality testing, per FDA requirements. While the shipment waits to be quality tested, it needs to be stored in the warehouse as well. At Amgen, this additional time is called "test and release time," and was accounted for in the model by converting the amount of time into an equivalent number of pallets of storage of process stock. Process stock can be calculated by D*L, where D is the demand and L is the lead time.

Different materials require different amount of test and release time. The demand can be calculated from annual Amgen production targets, and the lead time is given by the material type. For simplicity, a conservative estimate was made for test and release: all materials (including chemicals, resins, and cell culture media) were assigned 45 days except for disposables, which were assigned 3 days.

4.2.2 Data Collection for the Model

A significant amount of data was collected to develop the model and improve model accuracy: ASM long-range plan, Bill of Materials for manufacturing of drug substance, pallet conversion number, and test and release time.

ASM long-range plan: the production forecast for ASM, which specifies the number of drug substance batches the site needs to manufacture each year. The plant manager and his team use these annual targets to plan the weekly production schedule for the site, the Amgen run rate, the number of weeks between manufacturing batches (units of weeks/batch).

Bill of Materials: also called the BOM, this is the list of raw materials, sub-assemblies, intermediate assemblies, sub-components, parts and the quantities of each needed to manufacture the drug substance. Materials at ASM fall into the following categories: cell culture media, chemicals, resins, and disposables, and the quantities of each are given in units based on the type of material: solid powder (grams), liquid (ml), or disposables (each).

Pallet conversion numbers: the number used to convert the material into an equivalent fraction of the pallet so that the amount of space occupied in the warehouse can be calculated. The accuracy of this number has a significant impact on model accuracy, especially for the materials that take the most space. Normally, pallet conversion numbers are straightforward to obtain, but only ballpark estimates were available for disposables. Additionally, ASM implemented a "pre-weigh" strategy for some chemicals, which also changed the pallet conversion number. Pre-weighed chemicals were pre-packaged in the amounts to be added in the manufacturing process per special arrangement with the supplier, and therefore, often occupied significantly more space than normal packaging. This was taken into account in the calculation of pallet conversion numbers for these materials.

4.2.3 Additional Accommodations for Site Operations

Accommodations for additional storage were made for site operations: reject cage, consumables storage, and quality testing space.

Reject cage: designated for temporary storage of materials that failed quality testing.

Consumables: also called non-BOM, because these materials are not in the BOM, this area holds materials such as gloves and cleaning supplies.

Quality testing space: designated for holding test samples of incoming shipments for quality testing, this space needs to be located in the controlled room temperature area, ideally near the shipping dock for easier access, since every incoming shipment is required to be tested.

4.3 Model Elements and Functionality

This section will review the primary elements and functionality of the Warehouse Capacity Model. The model was developed using Microsoft Excel to allow for rapid development and revisions. The user inputs a few parameters in the input section to easily calculate the total pallets of storage and percent utilization of the warehouse. This section provides a walkthrough to illustrate the steps required to run the model, with screenshots.

User input (Figure 9)

1) Enter information on batches: run rate, and types of drug substance to be made

2) Verify warehouse pallet capacities and pallet fraction: storage capacity for each storage area, amount of each storage area to reserve for site operations, and the desired pallet fraction (if there is the ability to store multiple raw materials in one pallet space, how far each pallet can be divided)

3) Adjust desired order frequency, forward coverage (safety stock), test/release time, and lots to hold at supplier (this number is subtracted from total pallets).

Figure 9. A screenshot of the user input screen

User Input				
1) Enter information on batches				
Run rate	0.50	weeks		
Drug 1	8	lots		
Drug 2	0	lots		
Drug 3	0	lots		
2) Verify warehouse pallet capacities and pallet fraction (or leave at default)				
	Total Pallets	**Reject Cage/IQI**	**Non-BOM**	**Other**
CRT	564	25	50	0
2 - 8C	81	0	1	0
CRT Acid	16	0	1	0
CRT Base	16	0	1	0
CRT Flammable	10	0	1	0
2-8C Flam cab (L)	1360	0	1	0
Pallet Fraction:	0.5			
3) Adjust desired order frequency, forward coverage, test/release time (default below)				
Order Frequency	12	weeks		
Forward coverage (Safety Stock)	4	weeks		
Test/Release for chemicals	45	days		
	One-time buy	**Reordering**		
Lots to Hold at Supplier (VMI)	4	8	lots	

Warehouse usage projections

View the projected usage for a one-time buy inventory policy as well as a reordering policy (Figure 10), in units of pallets and capacity utilization. This section displays usage for information for the following conditions:

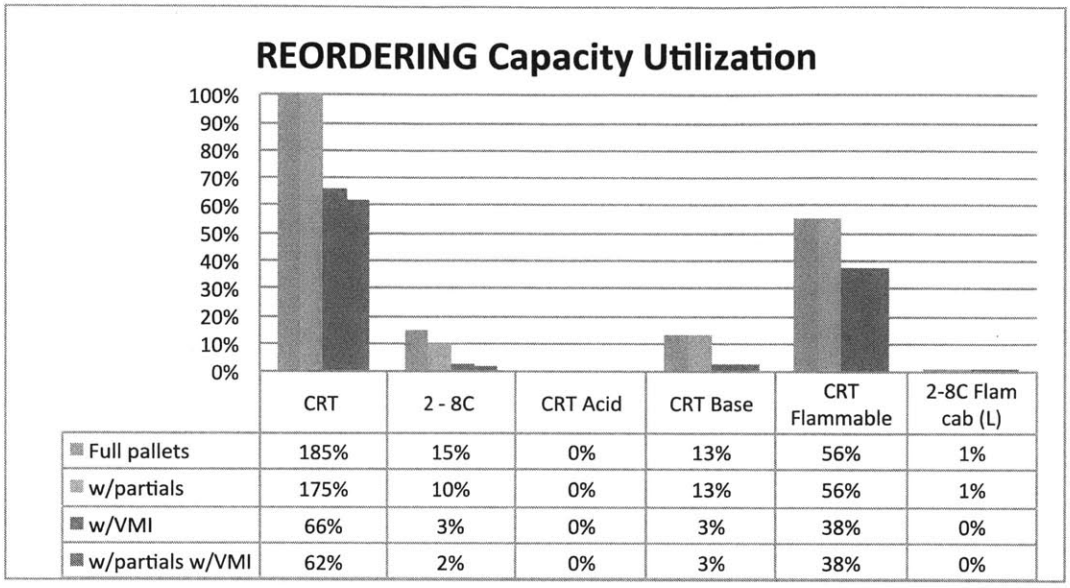
- Full pallets only
- With partial pallets - applies the pallet fraction specified in the input step
- With VMI (Vendor Managed Inventory) - applies to material held at supplier
- W/partials W/VMI – applies both conditions above

Figure 10. Sample output of warehouse usage projections, with reordering policy

Warehouse usage with reordering policy				
Pallet count	**Full pallets**	**w/partials**	**w/VMI**	**w/partials w/VMI**
CRT	907	857	322	305
2 - 8C	12	8	2	2
CRT Acid	0	0	0	0
CRT Base	2	2	0	0
CRT Flammable	5	5	3	3
2-8C Flam cab (L)	8	8	2	2
Total	926	872	328	310
	Total partials:	110		
Capacity Utilization	**Full pallets**	**w/partials**	**w/VMI**	**w/partials w/VMI**
CRT	185%	175%	66%	62%
2 - 8C	15%	10%	3%	2%
CRT Acid	0%	0%	0%	0%
CRT Base	13%	13%	3%	3%
CRT Flammable	56%	56%	38%	38%
2-8C Flam cab (L)	1%	1%	0%	0%

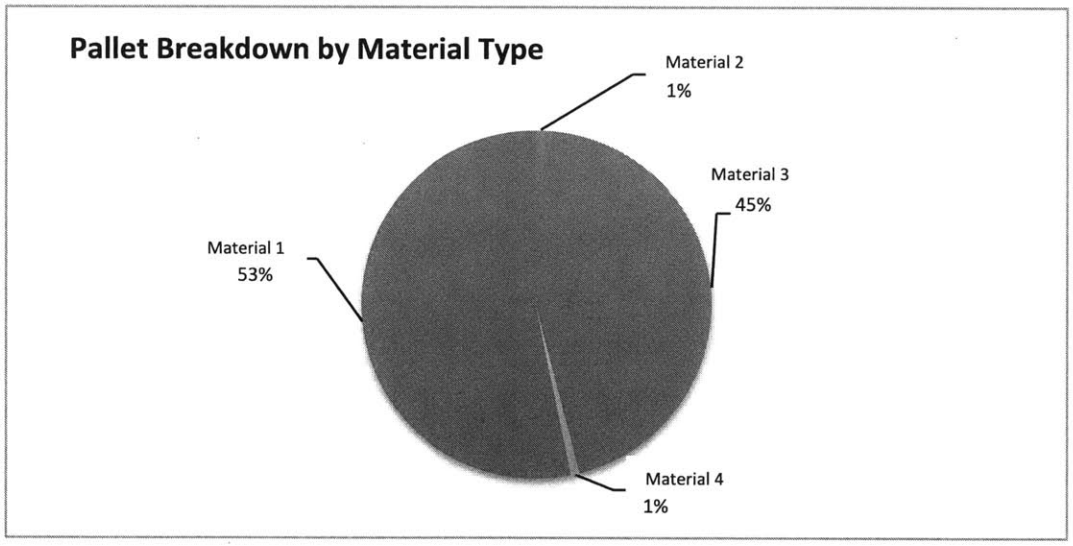
The model displays bar graphs of total pallet count (not shown) and capacity utilization (Figure 11). The model also displays the breakdown in the warehouse by material type (Figure 12) as well as the top 10 raw materials taking up the most space in the warehouse (Figure 13).

Figure 11. Sample output graph of capacity utilization



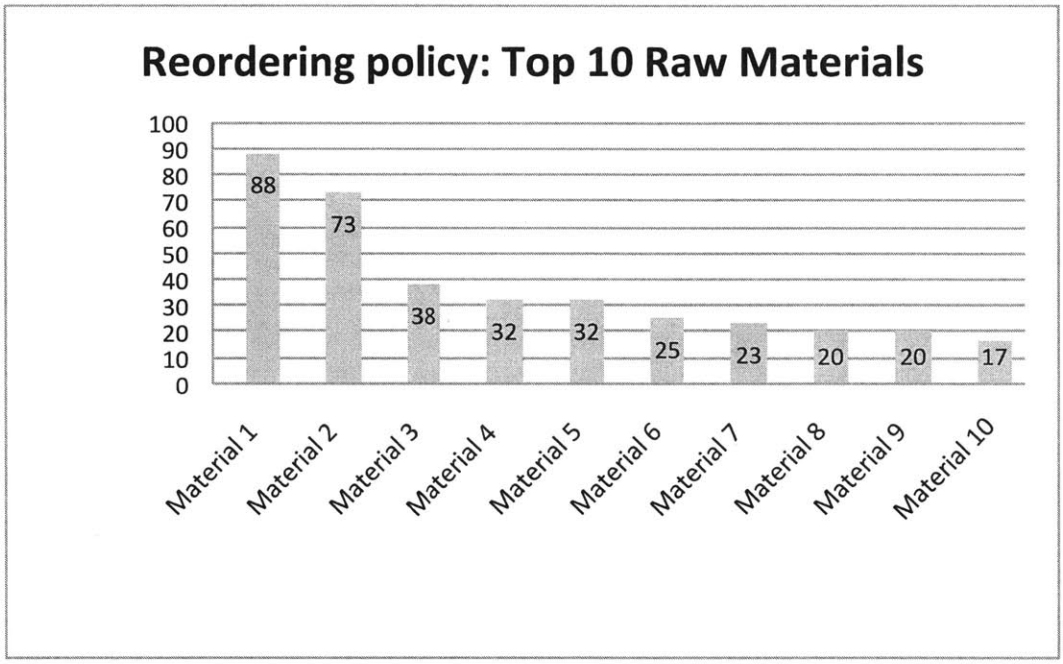
	CRT	2 - 8C	CRT Acid	CRT Base	CRT Flammable	2-8C Flam cab (L)
Full pallets	185%	15%	0%	13%	56%	1%
w/partials	175%	10%	0%	13%	56%	1%
w/VMI	66%	3%	0%	3%	38%	0%
w/partials w/VMI	62%	2%	0%	3%	38%	0%

Figure 12. Sample output material breakdown in the warehouse, by material type[6]



[6] Specific material names removed to preserve confidentiality.

Figure 13. Top 10 raw materials taking up the most space in the warehouse, in pallets



4.4 Process for Using the Model

In addition to the ability to calculate capacity utilization as described in Section 4.3, the model is a tool that enables the user to develop an inventory management strategy. The user may wish, for example, to adjust order frequency from 22 weeks to 12 weeks, to see the amount of improvement in capacity utilization. By just adjusting input parameters, the user can compare their effect on percent utilization to find those with the greatest improvement. Some other suggested parameters to adjust include run rate, safety stock, and the number of lots to hold at suppliers. The next chapter will describe in detail the specific recommendations for ASM operations strategy after applying the model.

4.5 Warehouse Capacity Analysis and Strategies to Improve Utilization

The ASM warehouse was originally designed to support full production and hold one month safety stock, but the Warehouse Capacity Model (see Chapter 4) shows the warehouse can only hold five manufactured drug batches[7] worth of cycle stock, and no safety stock (Figure 1). In the short term, ASM should implement a few operations strategize to improve capacity utilization. By 2018, ASM will need to utilize suppliers or Third Party Logistics Providers (3PL) to meet target production.

[7] Amgen manufacturing is measured in terms of manufactured drug "batches," not to be confused with a supply chain "batch," which is the amount of raw material in each order. To avoid confusion, a "batch" always refers to a batch of manufactured drug, while "order quantity" refers to the amount of raw material in each order.

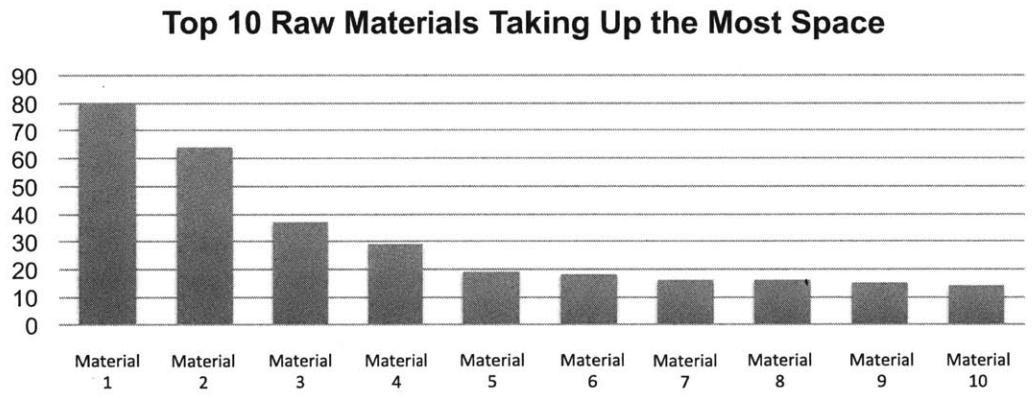
4.5.1 Operations Strategies to Improve Capacity Utilization

After analysis with the Warehouse Capacity Model, the following operations strategies were identified to have the greatest improvement in capacity utilization of the ASM warehouse: storing inventory with suppliers in 2015, and increasing frequency of delivery of materials. Additionally, an analysis was performed to compare two storage location assignment methods: random assignment vs. zoning, where random assignment was shown to be significantly more space-efficient.

Storing inventory with suppliers

In 2015, ASM should hold four manufacturing batches worth of inventory with suppliers who have warehouses in Singapore. Shipping locally from a warehouse in Singapore to ASM reduces lead time from a few weeks to 1 day, due to the shorter distance, and the removal of other potential delays, such as the time needed for customs clearance. As shown in Figure 14, holding 4 lots of inventory with the suppliers below who have warehouses in Singapore would open up CRT storage by 109 pallets, which is roughly 19% of the total capacity in the CRT storage area, the storage area at highest risk to reach 100% capacity utilization. One consideration with this strategy is that the inventory held at suppliers has not yet inspected, so a strategy needs to be developed to manage this risk.

Figure 14. Holding inventory with suppliers in Singapore significantly reduces storage required[8]



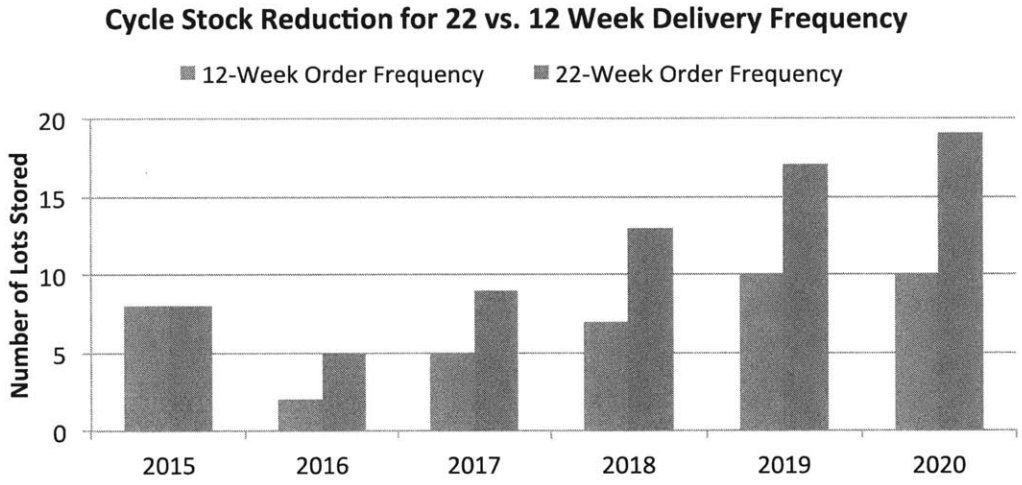
Supplier	A	B	C	D	E	F	G	H	I	J
Has Singapore warehouse?	X	X	X		X	X	X		X	X

[8] Material names and supplier names have been removed for confidentiality reasons.

Increasing delivery frequency

ASM should increase delivery frequency to reduce cycle stock. Because each incoming shipment is required to undergo quality testing, this strategy must be balanced with site and network material testing resources. The Warehouse Capacity Model indicates that increasing frequency from 22 weeks, a typical delivery frequency for many materials at Amgen, to 12 weeks, a delivery frequency that the staffing level at ASM can support, significantly reduces the amount of cycle stock that needs to be stored in the warehouse (Figure 15). ASM can further reduce the level of required cycle stock by increasing their staffing level in order to support a higher delivery frequency.

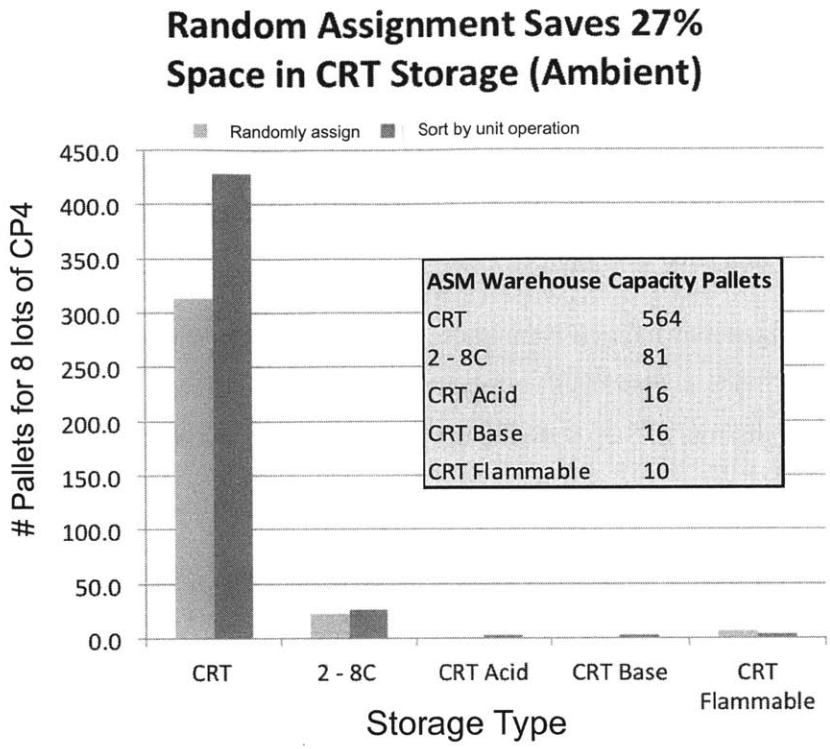
Figure 15. Delivery frequency reduces cycle stock



Random assignment vs. zoning

An analysis was performed to compare the capacity utilization of random assignment as compared with zoning by unit operation. Random assignment storage location assigns incoming shipments to any open location, while zoning assigns to its respective zone. In this analysis, the warehouse was divided into "zones" by unit operation. The same raw material is used in multiple unit operations, requiring storing the same raw material in multiple zones, which reduces efficiency. Random assignment instead of zoning saves 27% storage space (Figure 16). Given the space constraints of ASM warehouse, random assignment is recommended due to the savings in space. Note: using half pallets and small totes further maximizes capacity, because many raw materials are needed in small amounts.

Figure 16. Random assignment instead of zoning saves 27% storage space



4.5.2 Storage Options for ASM

Even with operations strategies, ASM will reach capacity by 2018 (Figure 4). Two storage options for ASM are with suppliers and a 3PL (Third Party Logistics Provider), so ASM needs to determine how much to store at each. Both provide advantages and disadvantages. The benefits of holding materials at 3PL are that 3PL's typically have a large amount of storage available and all the materials can be stored with one provider. However, they cost at minimum $500/pallet/year, which can become more costly, especially in the next 5-10 years, when target production for ASM is high. The benefits of holding materials with suppliers are that suppliers are incentivized to provide some storage, often at minimal or reduced cost. However, they usually have a limited amount of storage available, and materials would be spread out over many suppliers, which could be harder to manage logistically. In both cases, the raw material held has not yet been inspected, so a strategy needs to be developed to manage the quality testing of these materials. One strategy could be to perform a preliminary vendor site inspection of material and lot number or package integrity to reduce risk.

4.5.3 Future Directions: Maximizing the Benefit of Warehouse Capacity Models

Once the model was developed, it was used to assess the capacity of a new proposed warehouse at ASM, demonstrating that the Warehouse Capacity Model can be modified to guide the development of other warehouses across the company. While the manufacturing process for this new warehouse was different, the model used the same inventory management principles. The key finding is that the new warehouse will exceed maximum capacity in the flammables storage area. Fortunately, this was flagged early in the design phase for this warehouse, so the team was alerted early enough to be able to make decisions to accommodate the anticipated overage.

Table 5 shows the anticipated overage in flammables storage. The steps shown are manufacturing steps in the drug manufacturing process. Flammables storage is anticipated to exceed the maximum capacity of 21 pallets in Steps 1 through 4, Step 2 having the highest capacity overage.

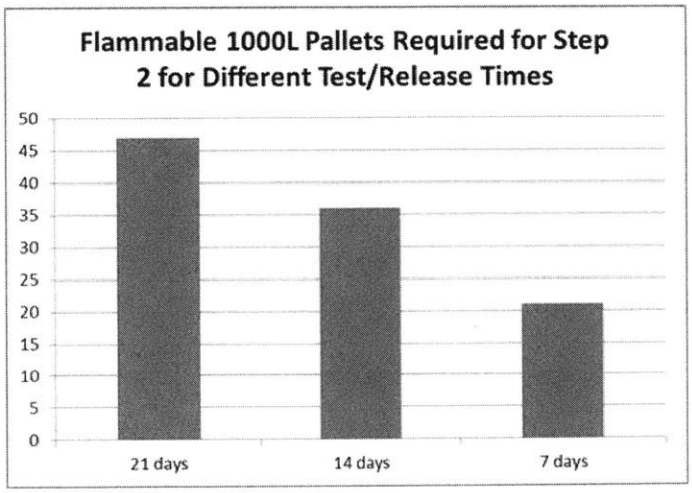
Table 5. Model enables warehouse decisions for additional warehouse at ASM

	Capacity	Step1	Step2	Step3	Step4	Step5
CRT	**6 pallets**	0	4	1	0	4
2 - 8C	**12 pallets**	2	3	3	2	3
Acid/Base (L)	**1364 L**	168	66	23	162	28
Flammable (1000L)	**21 pallets***	34	47	33	26	10
Flammable (200L)	**8 pallets**	1	1	0	2	2

*Each 1000L container = 1 pallet

As shown in Figure 17, reducing test and release time for step 2 from 21 days to 7 days can help the site stay under capacity. Otherwise, the site will need to identify other methods of storage to accommodate the overage. Identifying the issue in the warehouse design phase has enabled the team to make decisions to accommodate the anticipated overage.

Figure 17. Reducing test and release time reduces the amount of storage required



5 Transport Qualification of Disposable Bioreactor Bags

Transport risk mitigation for disposable bioreactor bags is critical to the manufacturing process; even a pin-sized hole in the bag can lead to contamination of an entire batch, and millions of dollars of lost revenue. ASM is using novel disposable, single-use bioreactor technology throughout their drug manufacturing process. Currently, suppliers don't complete transport qualification for custom assemblies and disposables. There is a need to assess and mitigate the risk, in terms of both cost and lead time. A gap assessment is required for raw materials from suppliers. To reduce the shipping risk to these bags, a 12-member, cross-functional team of experts at Amgen was formed, consisting of experts from Materials Science, Supply Chain, Global Strategic Sourcing, Transportation, and Supplier Quality Management, and Process Engineering, to partner with suppliers to establish a transportation qualification plan. Transport risk mitigation of bioreactor bags also reduces the required amount of storage, since fewer bags will need to be stored as safety stock. The transport qualification of bioreactor bags was successfully executed, and the process was documented in "Amgen Guidelines for Transportation Qualification of Single-Use Materials," to guide future transportation qualification plans for disposables.

5.1 Selection Criteria: Identifying High-Risk Materials for Qualification

Transport qualification is recommended for high-risk disposable materials. The following criteria was used to assess the level of risk associated with the disposable material. Materials that met several or all of the criteria were selected for transportation qualification.

- *Cost of material is $3000 or higher*: the cost of materials range from a few hundred dollars a piece to over $10,000; materials costing $3000 or more were flagged to be high-risk
- *Lead time of 90 days or more*: some disposables consisted of complex assemblies of many materials, contributing to the higher lead time to manufacturing and ship the product
- *Custom materials*: some disposables, such as wave bags, are made off-the-shelf, whereas other materials are customized for Amgen, which poses a higher supply risk, because it cannot be easily made by other suppliers, and often also has a higher associated lead time for manufacture
- *Critical to the drug manufacturing process*: materials that are used to manufacture batches of drug are the highest risk, because in addition to the associated replacement cost of a material failure, there is also risk to the drug batch itself, which can lead to the loss of millions of dollars of revenue
- *History of transportation issues*: some materials already had a history of damage from shipping, so these were flagged as high risk as well

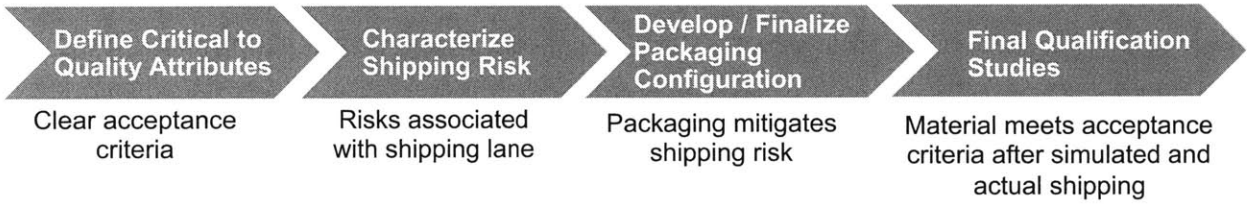
For this project, the 2000L bioreactor bag was selected because of its high cost, its lead time of nearly 90 days, the fact it is an Amgen custom material, and that it is critical to the drug manufacturing process.

5.2 Transport Qualification Steps Taken for Disposable Bioreactor bags

Transportation can be validated, just like any other process. The transport qualification process was presented at Amgen by Hutchinson and Stephan in 2006. In the Define phase, environmental characteristics that can impact product are identified, packaging design requirements are created, and transport lane attributes are identified. In the Design phase, packaging components and standard operating procedures are developed. In the Characterize phase, test profiles are created and the product is characterized for transport. In the Validate phase, packaging components and transport lanes are qualified, and operational (in-lab testing of anticipated extremes) and performance (field test shipments) qualifications are performed. Lastly, the Monitor phase covers change control and metrics.

Figure 18 shows the steps that were taken by the cross-functional team to develop transportation qualification for the 2000L bioreactor bag, and the specific steps taken were outlined below.

Figure 18. Schematic diagram of transport qualification steps



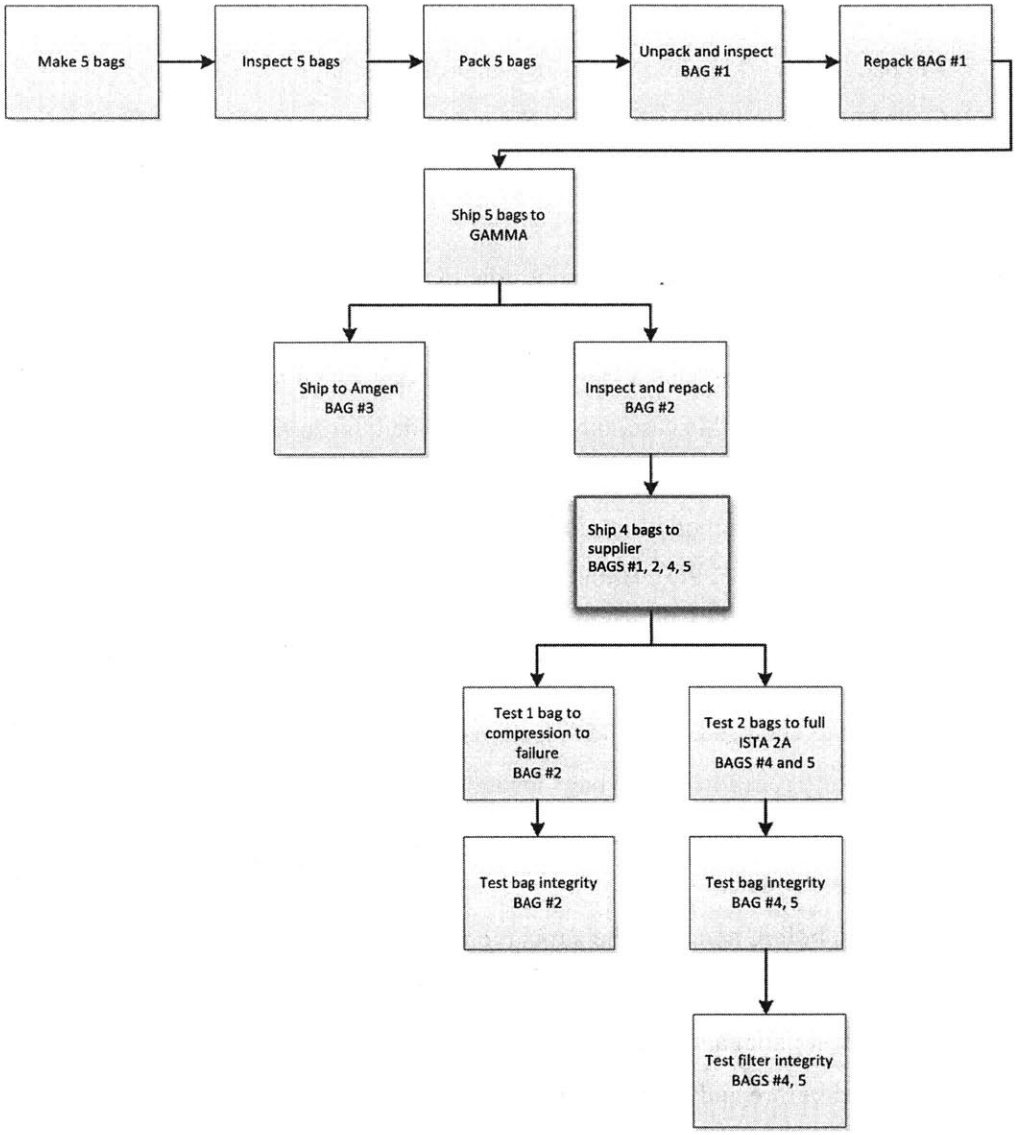
Steps to develop the transportation qualification plan for the 2000L bioreactor bag

1. Critical to Quality Attributes: the attributes of the bag that are tested before and after shipping to ensure the quality of the bag was maintained throughout transportation
   - Bag integrity – to ensure bag integrity, there must be no detectable leakage with snoop test
   - Filter integrity – to ensure the filter remained intact, the bubble point must be at 16 psi
   - Visual defects on the bag
   - Pits: The number of "pits" on the bag must be 10 or less, and each pit can only be at most 0.40-2.00 mm^2 in size, i.e. none can be greater than 2 mm^2
   - Gels: The number of "gels" can only be 10 or less, and each one can only be 0.80-3.00 mm^2 in size, i.e. none can be greater than 3 mm^2
   - Scratches/creases were noted, although the limits were not set

2. Characterize shipping risk: analysis of the specific characteristics of the shipping lane to determine the transportation risk to the bag
    - High temperature: the package (with the bioreactor bag enclosed inside) must be able to withstand up to 38C, due to the high temperatures in Singapore
    - High humidity: the package must be able to withstand up to 85% relative humidity, given the high humidity in Singapore
    - Shocks/vibrations from shipping: the package must be able to withstand shocks and vibrations from the origin (East Coast U.S.) to the destination (Singapore) per ASTM and ISTA standards
3. Develop/finalize packaging configuration: the packaging should be developed to meet the requirements defined in steps 1 and 2; in this case, the supplier decided to use existing packaging
4. Final qualification studies: there are two types of qualification studies, a simulated shipping study, which is called a transportation operational qualification (TOQ), and an actual test shipment, called a transportation performance qualification (TPQ). Both types of qualifications were performed for the 2000L bag, with the specifications outlined below.
    - Shipping simulation (TOQ)
        - The package, with the bag enclosed, and a 75lb load placed on top to simulate the second bag (to simulate the pallet configuration of two bags loaded per pallet), was exposed to 72 hours at 38C at 85% RH, a series of compression, vibration, drop, and random vibration testing per ISTA and ASTM testing standards
        - The bags were inspected before and after the simulation, per the criteria outlined in step 1
    - Shipping test (TPQ)
        - A bag was placed on a test pallet and sent on shipping lane from Millersburg, PA to ASM
        - The bags were inspected before and after the simulation, per the criteria outlined in step 1

The overall test plan is shown in (Figure 19).

Figure 19. Overall test plan in flow diagram



5.3 Guidelines for Transportation Qualification of Disposable Technology

Traditionally, transportation qualification has not been done on disposables or custom assemblies. Given the entire drug manufacturing process at ASM utilizes the novel, disposable technology, and will also be used at many other sites at Amgen, documenting the process and providing the lessons learned can help guide development of transportation qualification plans for all disposables. This section identifies lessons learned from developing the transportation qualification of the 2000L bioreactor bag.

1. Defining critical to quality attributes: Must align on specific criteria and test methodology with the supplier to ensure the qualification results can accurately measure the mitigation of transport risk.

2. Characterizing shipping risk: Ensure all risks associated with shipping lane are captured and tested. In this case, Amgen cross-functional team confirmed with the supplier that the materials should be tested under the high temperatures and high humidity of the Singapore climate.
3. Developing and finalizing packaging configuration: Design packaging that mitigates risks to the critical to quality attributes for the material from shipping risks that were identified.
4. Final qualification studies: Ensure that test packaging configuration is the same as the actual planned configuration, and ensure the test shipping lane matches the actual shipping lane. In this case, test shipment only contains one box per pallet, but actual shipments to ASM will stack two boxes per pallet. Also, while the actual material will ship directly from the supplier's distribution center, the test material was shipped from a city which is next to, but not the same as the city where the distribution center is located.

5.3.1 Bag Integrity Testing

The current transportation qualification plan called for a "snoop test" to check for leakage:

Snoop Test: Fill bag with 5 liters of water and then fill bag with air to 0.3 psi. Let the bag sit for 2 hours. Apply snoop around bag seams and cosmetic anomaly area to check if there is any leak. Roll the bag to allow water to reach bag seams and cosmetic anomaly area and check if there is any water leakage. Record result. Any leakage in either inner or outer bag film should be recorded.

However, leakage measured by a snoop test may not be reproducible, and can also vary from operator to operator. For more precise results, a pressure decay method is recommended to assess the amount of leakage in a bag. The pressure decay method works by recording the amount of leakage in a high quality bag to determine the "acceptable" amount of leakage. Bags are then pressure decay tested; if a tested bag has a higher amount of leakage than the "acceptable" amount of leakage, then this bag is flagged for leakage. In comparison to alternative methods of leak detection, pressure decay yields quantitative information and measurable data points that can be recorded, and upon which decisions can be made. An additional benefit of the pressure decay method is that it is non-destructive, i.e. the test material, in this case the bioreactor bag, can still be used after the test. One such test that is commercially available is the inSITE Inflation and Integrity Test System, made by ASI. The test is an inflation test in which a bag is pressurized to a preset level. After the bag system has stabilized, the decay in pressure over time is evaluated to determine if a leak is present ("inSITE Point of Use Inflation and Integrity Testing" 2015). The decay in pressure is referred to as "Delta-P."

There are four distinct phases to the pressure decay testing process (Figure 20). During the setup procedure, the programs walk the user through a Validation Setup. The Validation is unique to each bag

and tank combination and is stored for future tests. During this phase, users are instructed to run a minimum of three or a maximum of ten successful bag tests and three to ten (intentionally) flawed tests. The Validation step provides the system with the acceptable Delta-P values for "good" bags as well as "flawed" bags. Once these values are stored in the system, the system can easily perform pressure decay tests on bags to quickly determine if there is unacceptable leakage in the bag.

According to ASI, each step is unique to pressure decay, and ultimately makes the placement and filling cycle easier for the operator and gentler to the bag. Due to the sensitivity of the inSITE system, the testing results can vary from any changes in external pressure, tank size or room temperature, so it is a vital rule of thumb to have a consistent environment for each setup and test.

Figure 20. Four phases of pressure decay integrity testing by ASI

1. INFLATION CYCLE

Inflation is the period of time in which the bag system is being pressurized to a predetermined test pressure through an onboard blower. The air is forced through a 0.2 micron (µm), sterilizing grade filter.

2. CHARGE TIME

During the charge time phase, the bag system stretches allowing any creases that may be present to unfold. If necessary, the blower will add air to maintain the initial predetermined test pressure.

3. SETTLE TIME

The settle phase is the time allowed for the volume of the bag system to change and stabilize due to stresses introduced by pressurization. The adiabatic temperature also stabilizes during the settle phase.

4. TEST TIME

The test time is the period during which the decay of pressure is measured and recorded. This decay in pressure will distinguish between a flawed and non-flawed bag system.

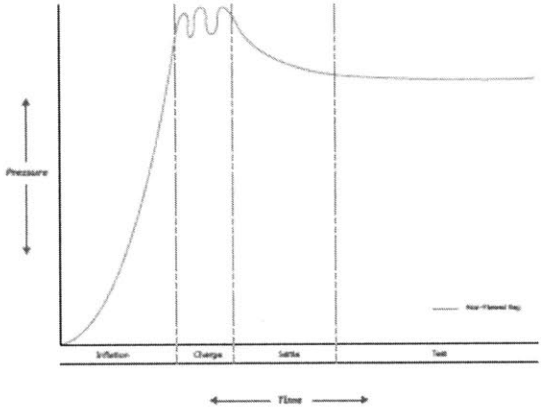


Figure 1: The four phases of the testing cycle of a non-flawed Bag.

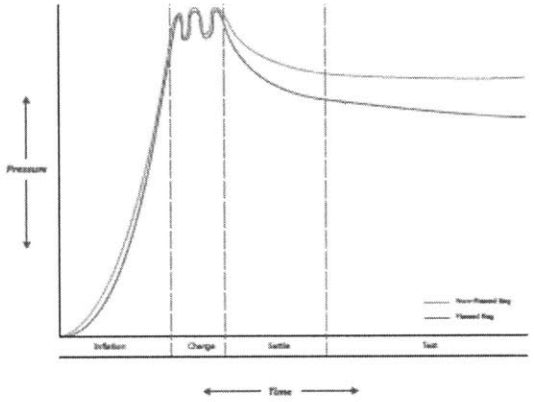


Figure 2: A comparison of a flawed bag and a non-flawed bag.

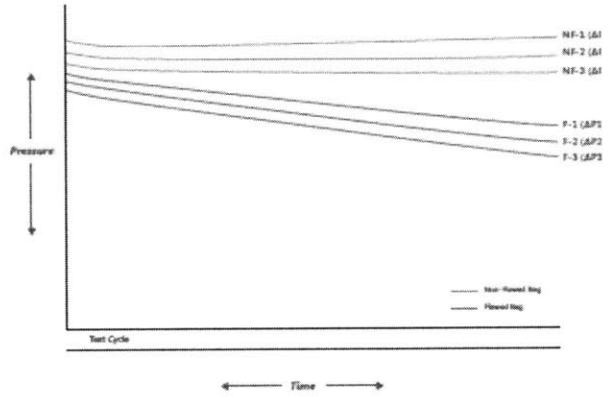


Figure 3: A comparison of the three successful bag tests and the three intentionally flawed bags. The measurements between the Delta P's for each will determine the allowable variance.

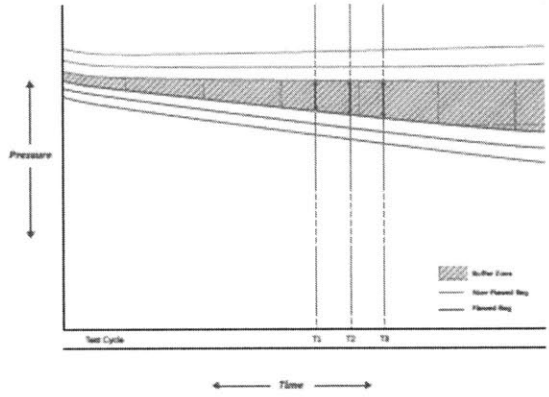


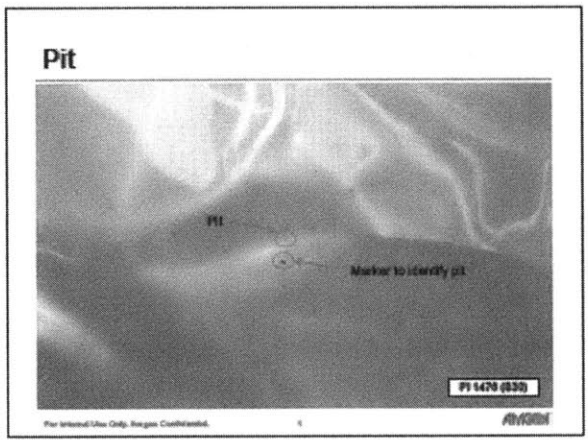
Figure 4: The variance between the highest Delta-P of a non-flawed bag and the lowest Delta-P of a flawed bag determines the buffer zone. The buffer zone is the established point of time for the fine leak flag. This also establishes the validated pass / fail point criteria.

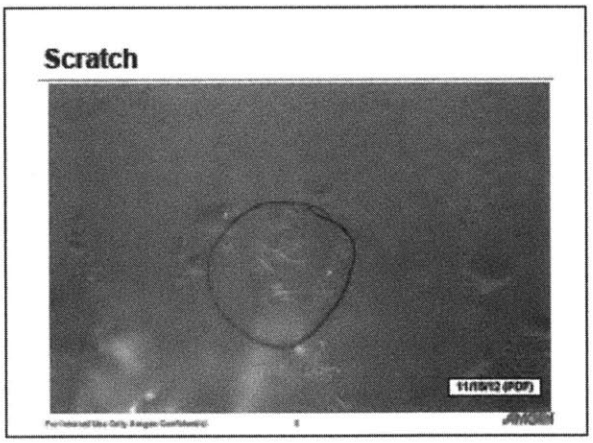
5.3.2 Visual Inspection

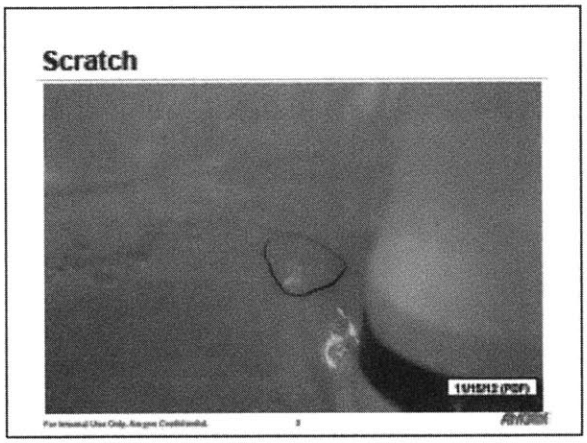
One critical issue that arose from the 2000L Transportation Qualification Plan was that visual inspections were difficult, because defects were not clearly defined. For example, one operator could interpret a crease on a bag as a defect and send it back to the supplier, when in fact the crease was a cosmetic defect. On the other hand, an operator could interpret the crease as a cosmetic defect, only to find the crease forms a leak during drug manufacturing, causing the loss of an entire drug manufacturing batch. A tool that could help operators identify defects quickly and accurately is the creation of a "visual library" of defects (Figure 21).

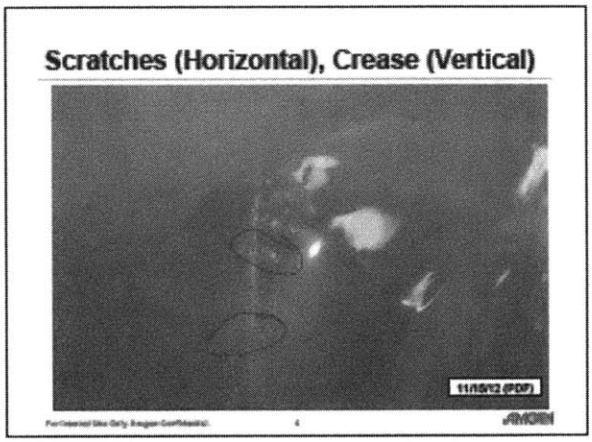
Additionally, this visual library could aid in troubleshooting of raw material defects. At the time of the development of the 2000L Transportation Qualification Plan, there were many other types of visual defects observed by the team, such as misaligned seals, and jagged edges, which may indicate the bag is defective, but which were not addressed in the plan. A visual library of defects observed could serve as a helpful tool to aid in discussions with suppliers.

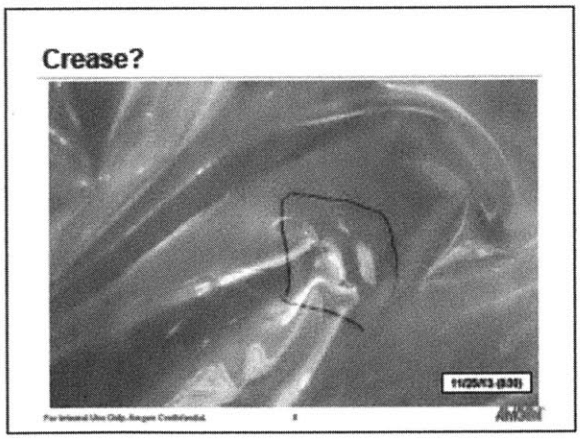
Figure 21. Visual library of defects

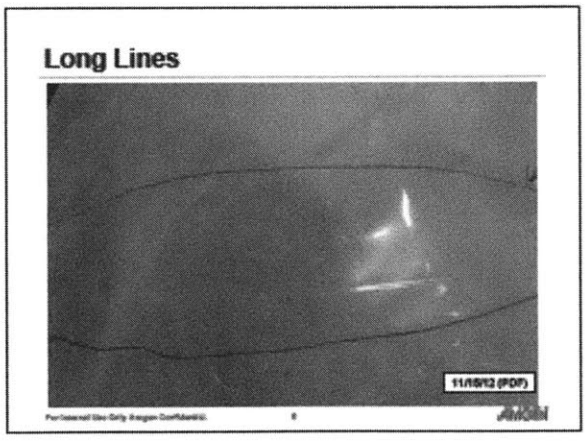




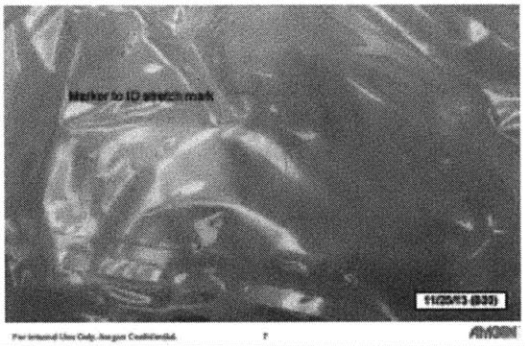




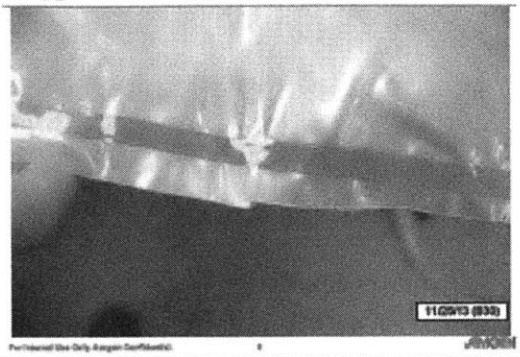




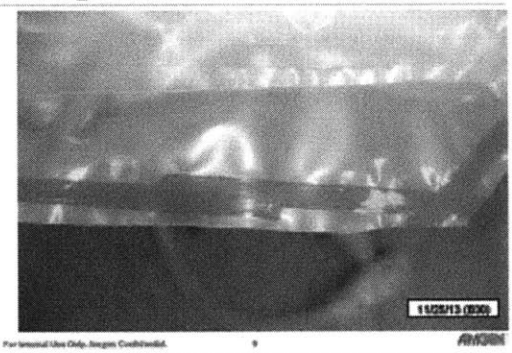
Long Lines



Jagged Cut



Misaligned Seal



6 Conclusion

The ASM warehouse is projected to reach capacity in 2017, increasing risk for the site and incurring the cost of outsourcing storage. A Warehouse Capacity Model was developed to assess capacity for the warehouse and identify operations strategies to improve warehouse capacity utilization. The model calculated the total average amount of inventory by summing the amount of cycle stock, safety stock, and process stock (quality testing and release of materials) in the warehouse.

In the short-term, ASM should implement the following to improve operations: store additional inventory with suppliers in Singapore, increase frequency of delivery of materials, and utilize random assignment instead of "zoning." First, temporarily storing materials with suppliers with warehouses in Singapore is the most direct way for ASM to reduce inventory in the warehouse. Suppliers who already have warehouses in Singapore should be prioritized because of reduction of risk in shipping lead time and quality testing. Shipping lead time from outside Singapore can take a few weeks, while 1-day delivery is possible when shipping locally within Singapore. Additionally, proximity to the warehouse means ASM can more easily implement a preliminary quality testing of inventory, if desired. Second, increasing frequency of delivery has a high impact on the amount of cycle stock due to the concept of "lot sizing:" a lower delivery frequency requires a higher order size, which increases the amount of cycle stock that must be stored in the warehouse to meet production levels. Given the high level of cycle stock required, and the increase in target production levels for the site over the next several years, ASM should try to reduce the amount of cycle stock required to store in the warehouse. Increasing from a 22-week delivery frequency (Amgen norm) to a 12-week delivery frequency (highest that ASM can support), for example, reduces the amount of required cycle stock by over 40%. Note that this strategy must be balanced with the required staffing level to support the quality testing of incoming raw material shipments, as each shipment must be quality tested, per FDA regulations. Lastly, given the space constraints of ASM, the site should utilize random location assignment instead of "zoning" by unit operation to save space. While zoning by unit operation could reduce picking time, random location assignment is more efficient in capacity utilization. Picking time is not expected to be an issue given the small size of the ASM warehouse, whereas the warehouse is space constrained, so random location assignment is recommended. An analysis showed that random assignment instead of zoning saves 27% storage space in the ASM warehouse.

However, even with these strategies in place, by 2018, ASM will need to determine how much to store with suppliers vs. 3PL. Suppliers can often provide storage at minimal or reduced cost but the amount of storage is limited. 3PL typically has a large amount of storage available, however they cost at minimum $500/pallet/year, which can become more costly, especially in the next 5-10 years, when target

production for ASM is high. In both cases, the raw material held has not yet been inspected, so a strategy needs to be developed to manage the quality testing of these materials.

For future warehouses, the Warehouse Capacity Model should be used for warehouse decisions earlier in the design phase, to give the team enough time to implement recommendations. This capacity model was used to assess the capacity of a new proposed warehouse. Identifying the issue in the warehouse design phase has enabled the team to make decisions to accommodate the anticipated overage.

Transport risk mitigation for disposable bioreactor bags is critical to the manufacturing process; transport risk mitigation of bioreactor bags also reduces the required amount of storage, since fewer bags will need to be stored as safety stock. The 2000L bioreactor bag was chosen as a high-risk raw material, and therefore a good candidate for transportation qualification, due to its high cost, a lead time of nearly 90 days, and the fact that it is an Amgen custom material, and it is critical to the drug manufacturing process. A 12-member, Amgen cross-functional team was created to develop and execute the transportation qualification plan for the 2000L bag, following steps from the Transportation Validation Lifecycle Planning Operational Training given by Hutchinson, Gary, and Andy Stephan at Amgen in 2006. Steps from defining critical to quality attributes to final qualification studies helped to establish a robust qualification plan. The transport qualification of bioreactor bags was successfully executed, and the process was documented in "Amgen Guidelines for Transportation Qualification of Single-Use Materials," to guide future transportation qualification plans for disposables. Key learnings outlined in this document were the recommended selection criteria to identify which raw materials were high risk and should have transportation qualification. Additionally, the pressure decay method is recommended for more robust bag integrity testing, and "visual library" of defects should be created to increase speed and accuracy of visual inspections.

References

"ASTM International - Wikipedia, the Free Encyclopedia." 2015. Accessed January 21. http://en.wikipedia.org/wiki/ASTM_International.

Choi, Jason Jinho. 2014. "Raw Material Inventory Planning in a Serial System with Warehouse Capacity." Massachusetts Institute of Technology. http://dspace.mit.edu/handle/1721.1/90775.

D10 Committee. 2009. *Practice for Performance Testing of Shipping Containers and Systems*. ASTM International. http://www.astm.org/doiLink.cgi?D4169.

D10 Committee. 2010. *Test Method for Determining Compressive Resistance of Shipping Containers, Components, and Unit Loads*. ASTM International. http://www.astm.org/Standards/D642.htm.

D10 Committee. 2012. *Practice for Performance Testing of Packages for Single Parcel Delivery Systems*. ASTM International. http://www.astm.org/doiLink.cgi?D7386.

D10 Committee. 2013. *Practice for Conditioning Containers, Packages, or Packaging Components for Testing*. ASTM International. http://www.astm.org/doiLink.cgi?D4332.

Gray, Ann E., Uday S. Karmarkar, and Abraham Seidmann. 1992. "Design and Operation of an Order-Consolidation Warehouse: Models and Application." *European Journal of Operational Research* 58 (1): 14–36.

Gu, Jinxiang, Marc Goetschalckx, and Leon F. McGinnis. 2007. "Research on Warehouse Operation: A Comprehensive Review." *European Journal of Operational Research* 177 (1): 1–21. doi:10.1016/j.ejor.2006.02.025.

Gu, Jinxiang, Marc Goetschalckx, and Leon F. McGinnis. 2010. "Research on Warehouse Design and Performance Evaluation: A Comprehensive Review." *European Journal of Operational Research* 203 (3): 539–49. doi:10.1016/j.ejor.2009.07.031.

Hausman, W.H., L.B. Schwarz, and S.C. Graves. 1976. "Optimal Storage Assignment in Automatic Warehousing Systems." *Management Science* 22 (6): 629–38.

Hutchinson, Gary, and Andy Stephan. 2006. "Transport Validation Lifecycle Planning Operational Training." Amgen, October 31.

"inSITE Point of Use Inflation and Integrity Testing." 2015. Accessed February 17. http://www.asisus.com/life-sciences/bioprocessing-products/point-of-use-integrity-testing.

"Leak Test Methods, Reference Leak Rates." 2015. Accessed January 21. http://www.schreiner-testing.it/index.php?IDcod=47&lang=uk.

"Monoclonal Antibody." *Wikipedia, the Free Encyclopedia*, March 26, 2015. http://en.wikipedia.org/w/index.php?title=Monoclonal_antibody&oldid=653594295.

Palmer, Eric. 2015. "Amgen Opens $200M Continuous Purification Plant in Singapore." *FiercePharmaManufacturing*. Accessed April 1. http://www.fiercepharmamanufacturing.com/story/amgen-opens-200m-continuous-purification-plant-singapore/2014-11-20.

"Prosensys – Measurement and Sensor Technology for Serial Production – Ultrasonic Leak Testing." 2015. Accessed January 21. http://www.prosensys.de/english/leak_rate_calculation.html.

"PSC Biotech- Life Science Service and Solution Provider." 2015. Accessed January 21. http://www.biotech.com/shippingValidation.php.

Schwarz, L.B., S.C. Graves, and W.H. Hausman. 1978. "Scheduling Policies for Automatic Warehousing Systems: Simulation Results." *AIIE Transactions* 10 (3): 260–70.

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

Snow, Daniel C., Steven C. Wheelwright, and Alison Berkley Wagonfeld. "Genentech - Capacity Planning." HBS No. 9-606-052. Boston: Harvard Business School Publishing, 2006.

"What Is Biotechnology?" Accessed April 1, 2015. http://biotechnology.amgen.com/biotechnology-explained.html.