Capacity Analysis, Cycle Time Optimization, and Supply Chain Strategy in Multi-Product Biopharmaceutical Manufacturing Operations

by

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B.S. Chemical Engineering, Purdue University, 2002

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

Master of Business Administration
and
Master of Science in Chemical Engineering

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

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Abstract

Application of system optimization theory, supply chain principles, and capacity modeling are increasingly valuable tools for use in pharmaceutical manufacturing facilities. The dynamics of the pharmaceutical industry – market exclusivity, high margins, product integrity and contamination constraints – coupled with increasing cost pressures, demand for specialized products increase, and growing industry complexity makes analytical business decisions necessary to sustain competitive advantage.

The united application of capacity modeling, system optimization, and supply chain analysis tools, paired with implementation strategies on a multi-product vaccine production system are detailed to address important business difficulties.

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Table of Contents

List of Figures

List of Tables

List of Equations

Glossary, Definitions, and Abbreviations

Table 1-1 Glossary, Definitions, and Abbreviations

Adjuvant	A substance that increases the immune system reaction to the antigen, and thus requires less antigen per patient to produce desired response (1)
Antigen	A substance that causes immune systems to produce antibodies against the substance (2)
Aseptic	Technique used to prevent infection (3)
Bid and Tender	The sale of bulk quantities of commodity product from the lowest bidder, typically a large organization such as a government.
BPR	Batch production records, documents used to record actions and parameters during manufacturing process
Buffer	A solution containing chemicals auxiliary to the product stream used in pharmaceutical manufacturing
Bulk	Description of type of manufacturing that produces the primary active ingredient or antigen in whole, purified form
Chromatography	A purification process used to separate waste from product in pharmaceutical manufacturing; often uses a resin and buffer
Conjugate	A protein joined with the polysaccharide to increase desired immune response (3)
Constraints	Mathematical statements that limit or impose requirements on the relationships between decision variables (4)
CS	Clean steam, a process utility used in manufacturing
Decision Variables	The unknown parameters which are to needed be determined (4)
Diluent	A liquid added to a vaccine to dilute or dissolve the antigen
EPQ	Economic Production Quantity
Exploratory Stress	Voluntarily creating a strained, atypical environment for a system to learn how the system reacts and fails under controlled circumstances, to then prevent future failures
FDA	Federal Drug Administration, United States
GUSEK	An open-source solver which uses GLPK
GLPK	A linear programming solver for windows
HHS	Department of Health and Human Services, United States
Hib	Haemophilus Influenza Type B
HVAC	Heating, Ventilating, and Air Conditioning; a process utility used in manufacturing
kanban	A signal-based system to visually indicate a need in a "pull" system of materials (5)

LGO	Leaders for Global Operations, a dual-degree program at Massachusetts Institute of Technology for an Master of Business Administration (MBA) or Master of Science in Management from MIT Sloan School of Management and Master of Science from the MIT School of Engineering
LTD	Lead Time Demand
Lyophilization	Freeze drying of a substance to remove water through sublimation and desorption (6)
Makespan	The duration of time to complete a job
mds	Million doses of vaccine, a unit of measure
Meningitis (Men)	An inflammation caused by an infection of the neurological protective membranes (1)
Menjugate	A vaccine for the treatment and prevention of meningococcus C infections caused by the pathogen Neisseria meningitides (7)
Menveo	A vaccine for active immunization to prevent meningococcal infections (Groups A, C, Y, and W-135) caused by *Nesseria meningitidis* serogroups A, C, Y, and W-135 (8)
MIT	Massachusetts Institute of Technology
NHS	National Health Service, United Kingdom
NICE	National Institute for Health and Clinical Excellence, United Kingdom
NVD	Novartis Vaccines and Diagnostics
Objective Function	Mathematical expression that incorporates the constraints to find the optimal result
Overfill	A small amount of excess material filled into a container above the specified amount of product to ensure sufficient material is available for dosing
P&ID	Piping and instrumentation drawings
Payors	Insurer, employer who provides employee benefit health coverage, or regional or federal government (9)
PFD	Process flow diagrams
Primary	Description of type of manufacturing that produces the primary active ingredient or antigen in whole, purified form
PW	Purified water, a process utility used in manufacturing
QALY, Quality-adjusted Life Year	A measure of the effectiveness of a pharmaceutical product or healthcare treatment accounting not only for the quantity of life but also the quality of life. A QALY is the arithmetic product of life expectancy and the quality of the life, as a fraction no greater than 1.0, representative of full quality of life. (10)
Resin	A material used in chromatography to purify products
Rosia, Italy	A small town about a half-hour drive from Siena, Italy in the Tuscan region

Secondary Manufacturing	A description of a type of manufacturing that is downstream of primary manufacturing that secures the material into a delivery mechanism (e.g. vial, capsule, tablet)
Sensitivity Analysis	Review of how the solution to a mathematical problem changes when the constraints and assumptions are relaxed
Serotype	A group of related microorganisms with a common set of antigens (3)
SME	Subject matter expert
SOP	Standard operating procedures
Syringe, Pre-filled Syringe	A delivery device used to inject fluid into the body (3); vaccine delivery presentations include syringes which are pre-manufactured with product
Vaccine	Immunization that contains weakened or dead organisms that create immunity in the body against diseases without introducing the disease
Valent	Description for the mechanisms of action of a product (e.g. monovalent, multivalent)
Value Stream	The necessary activities in a process that create or add value to a customer (11)
Vial	A small, closed vessel for liquids (3)
WFI	Water for Injection, a process utility used in pharmaceutical manufacturing
WIP	Work in Progress
WHO	World Health Organization
$\forall(x, y)$	Mathematical symbol representing "for all" in set x and y

1. Introduction

1.1. Project Situation

This thesis is the result of a six and a half month internship with Novartis Vaccines in Rosia, Italy as a fellow in the Massachusetts Institute of Technology Leaders for Global Operations program. The internship is a research-based component of the two year dual-degree program for a Master of Business Administration and a Master of Chemical Engineering.

The active ingredient multi-product vaccine facility in Rosia, Italy currently makes five different bulk products, or intermediates, for several vaccine products and is the launch facility for new bulk vaccines. Currently the facility is not capacity constrained, but production requirements will increase with the growth of current products and introduction of new products.

1.2. Project Overview

The Bacterial Operations bulk active ingredient production facility in Rosia, Italy currently material product for three products, Menveo (Meningococcal A, C, W-135, and Y), Menjugate (Meningococcal C), and Haemophilus Influenzae Type B (Hib). The Rosia Bacterial Operations facility currently operates under full production capacity. As the primary launch facility for many new Novartis Vaccine products, the management seeks to better understand the operational capabilities and facility constraints. Additionally, through cycle time reduction, processing improvements, scheduling optimization, and supply chain strategy, operating capacity can be increased.

This situation is reviewed in three primary components.

- A model of facility capacity for analysis of the introduction of new molecules and evaluation of the impact of increased production of existing products.
- A system optimization function to review production scheduling for operational improvements and evaluation of theoretical bottlenecks.

- Supply chain analysis for analytical determination of key parameters, including changeover frequency, reorder point, demand production needed, inventory levels, economic production quantity, and lead time production demand.

In this thesis, proprietary data has been disguised; example data is provided for explanation of ideas and concepts only.

1.3. Project Motivation and Impact

The Rosia Bacterial Operations is a manufacturing launch facility for new products, and is an important site for the growth of Novartis Vaccines. The facility was acquired by Novartis with the 2006 acquisition of a vaccine company named Chiron. Improvements across the newly formed Novartis vaccine division are progressing with significant investment from Novartis.

1.3.1. Project Goals

The goals of the project include first increasing understanding of the facility capabilities, and then applying the understanding to operational improvements. Through modeling and capacity analysis, restrictions of the facility and operational opportunities are identified. Scheduling decisions are compared for options between various scenarios within long-range schedule planning. Also, opportunities are identified for production improvements through operational efficiencies and strategic supply chain changes, including product changeover and location of inventory holding throughout the manufacturing value chain.

1.3.2. Impact of Project

The implementation of these changes has strong effect on analytical decision-making within the manufacturing strategy group. The data produced is particularly important for evaluation of in-house capacity, additional capacity expansion decisions, and consideration of third-party outsourcing manufacturing options.

Within the facility, several strategies can be aligned to the results of this project. Capital investments and improvement projects can now be better focused to critical areas with most value for the effort towards increasing flexibility and capacity. The projects also focus on opportunities to improve cycle time and production output in these key areas. The supply chain

calculations identify where to best strategically place inventory, where to eliminate non-value added inventory, and how to obtain the most value for each unit of changeover cost. These changes are crucial to increasing the benefit to the organization of the existing production assets and resources. Modeling current capacity, evaluating production scenarios, and optimizing cycle time will increase production understanding throughout the organization.

1.4. Thesis Overview

This thesis will begin with a review of the pharmaceutical industry, including specific dynamics special to the vaccine business. An overview of Novartis background and history of the vaccines division of the company will follow, with particular emphasis on the Bacterial Operations in Rosia, Italy. Next, the approach to the problem is presented with supporting research theory tied with overarching project methodology. Key conditions, variables, and constraints are introduced here to create a unified approach across the techniques of analysis.

The first of three detailed techniques presented in this thesis is capacity analysis and simulation, including defining capacity, modeling and simulation approach and techniques, political dynamics of modeling, and the implications of modeling results. Following model development, validation, sensitivity analysis, model recommendations, and using exploratory stress tools are reviewed.

Cycle time improvement techniques are reviewed through the development of an optimization function. Development plan and strategies are reviewed with a detailed presentation of the equations and model development, and how these tools are applied to improve operational capacity.

In the following chapter, the supply chain is reviewed for products from the Bacterial Operations facility in Rosia. Essential supply chain parameters are calculated, including economic production quantity, product changeover frequency, production batches needed, safety stock of inventory, and optimal number of campaigns per year. Risk balancing, inventory holding strategy, and demand uncertainty topics are explored.

Lastly, organizational dynamics and change implementation techniques are reviewed as an important factor in success to project implementation. In conclusion, recommendations are presented, uniting the multiple forms of analysis used across the project.

2. Overview, Current Challenges, and Manufacturing Strategy

2.1. Industry Overview

As described by Fine in *Clockspeed*, the pharmaceutical industry began with a "sleepy" rate of change, strong growth, and high barriers to market entry (12). Pharmaceutical products take nearly a decade to be discovered, tested, validated, and approved for sale. Particularly with the introduction of biopharmaceutical products, the double-helix described by Fine has progressed to strong horizontal and modular integration with many partnerships, enhancing the ability to leverage cross-functional skills and produce products more quickly. This change in complexity comes not just with increasing speed, but also increased regulations across developed countries and the beginning of emerging market regulatory agencies. The industry demand is also expanding as the rate of consumption in emerging markets increases.

2.1.1. Costs and Importance

One of the most significant factors in the future of the industry is cost. The financial expense and benefit of pharmaceutical products dictate the global approvals by regulatory agencies, payors, and significantly impact capacity requirements for manufacturing.

As described by Berndt, "Access to health care is considered by many to be a personal right or universal entitlement, unlike access to other goods and services," (9). The pharmaceutical industry represented about $550 billion of healthcare costs, or about 10%, in 2007 (13). The cost of pharmaceutical products lead the increase in health care expenses in the 1990s (14), and grew at a rate of 9.4% from 2001 to 2006, more than twice the annual rate of inflation (15). Increasing life expectancy and aging of the population average heightens impact and emphasis on health care reform and cost reduction. However, many opportunities exist across the pharmaceutical value and distribution chains to improve service levels, efficiencies, and reduce costs to customers and payors (13).

In particular, two factors which are progressively influencing health care cost management in developed countries are "QALYs" Quality Adjusted Life Years and prevention

versus treatment care. These will strongly impact the approval and uptake of pharmaceutical, biotech, and vaccine products. In turn, this will impact the amount of product demand needed from manufacturing and also increase demand uncertainty and difficulty of manufacturing capacity planning.

2.1.1.1. Quality Adjusted Life Years (QALYs)

The United Kingdom's National Health Service (NHS) created NICE, the National Institute for Health and Clinical Excellence in the 1990s to address concerns about the health care industry in the UK.

Table 2-1 Reasons for Creation of NICE (16)

Slow uptake of new technologies and practices
Widespread variation in the nature and quality of care
Growing public concern and increasing media criticism
Government commitment to improve the quality and range of care
Prospect of significant reinvestment in the NHS: plan to grow from about 6.5% to about 9% of GDP

A primary purpose of NICE is to provide guidance based on not only clinical effectiveness but cost effectiveness. The organization is designed to increase education to more informed consumers and provide increased value to the health care network (16).

The QALY measurement is used by NICE to gauge the quality of life improvement gained with a treatment option, and then used to compare treatment options with cost consideration. This factor is then multiplied by the duration of life for an overall QALY value. An example of how the quality of life is determined against five categories of health is presented in Table 2-2. For a more detailed introduction into the calculation of QALYs, refer to *What is a QALY?* (10).

Table 2-2 Quality of Life Valuation by Health State *(Adapted from Phillips)* (10)

Health State Description	Quality of Life Valuation
No problems	1.000
No problems walking about; no problems with self-care; some problems performing usual activities; some pain or discomfort; not anxious or depressed	0.760
Some problems walking about; some problems washing or dressing self; some problems with performing usual activities; moderate pain or discomfort; moderately anxious or depressed	0.516
No problems walking about; some problems washing or dressing self; unable to perform usual activities; some pain or discomfort; not anxious or depressed	0.329
Some problems walking about; no problems with self-care; no problems with performing usual activities; moderate pain or discomfort; extremely anxious or depressed	0.222
Some problems walking about, unable to wash or dress self, unable to perform usual activities, moderate pain or discomfort, moderately anxious or depressed	0.079
Death	0.000
Confined to bed; unable to wash or dress self; unable to perform usual activities; extreme pain or discomfort; moderately anxious or depressed	-0.429

Because of this, a unit of currency/QALY is frequently used to compare treatment regimens and recommendations for approval of use, as shown in Figure 2-1.

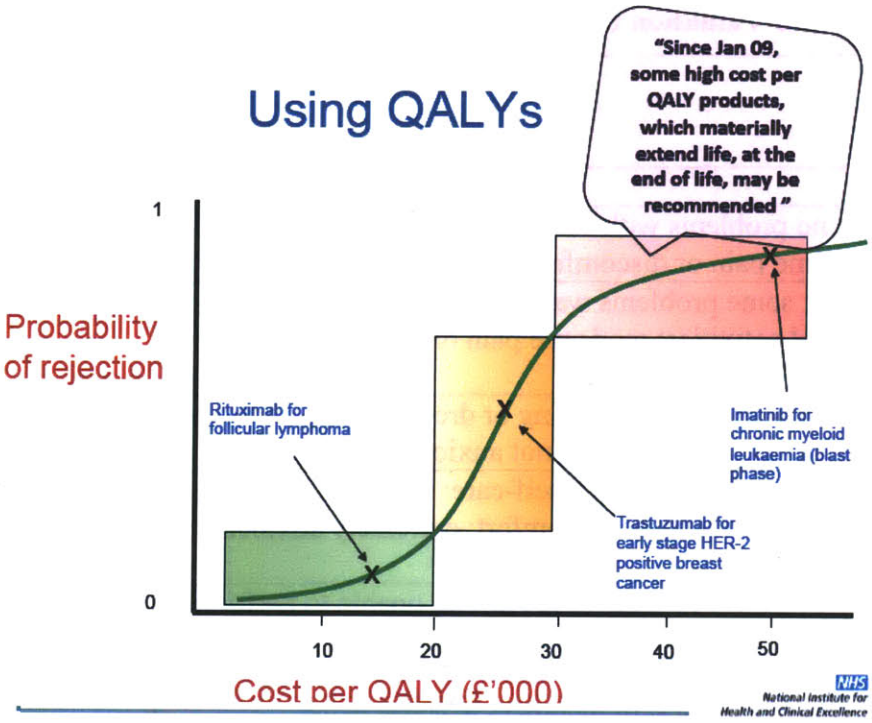


Figure 2-1 Cost per QALY as Measure of Treatment Approval (16)

However, this analysis is not without controversy. Execution of practice shows that companies may strategically place the price of products just high enough to be recommended for approval based on cost per QALY. The cost per QALY parameter also creates a controversial stance of the cost of human life and that a life has an upper-bound of value. As quality-based metrics of efficacy such as QALYs become more popular world-wide, this will have a strong impact on the needed manufacturing capacity of health care products.

2.1.1.2. Prevention versus Treatment

In society, there is often a resource pull between the treatment of disease-afflicted patients versus allocating resources for prevention. As shown within a system dynamics model in Figure 2-2, the cycle of diabetes prevention and treatment are interrelated. The amount of total resources is limited; therefore, the amount of money spent on treatment of current patients diminishes the amount of funds available for disease prevention in healthy people. This over time creates a cycle of worsening diabetes epidemic over time, called a negative reinforcing

loop. (For additional information on system dynamics modeling, refer to Sterman, *Business Dynamics* (17).)

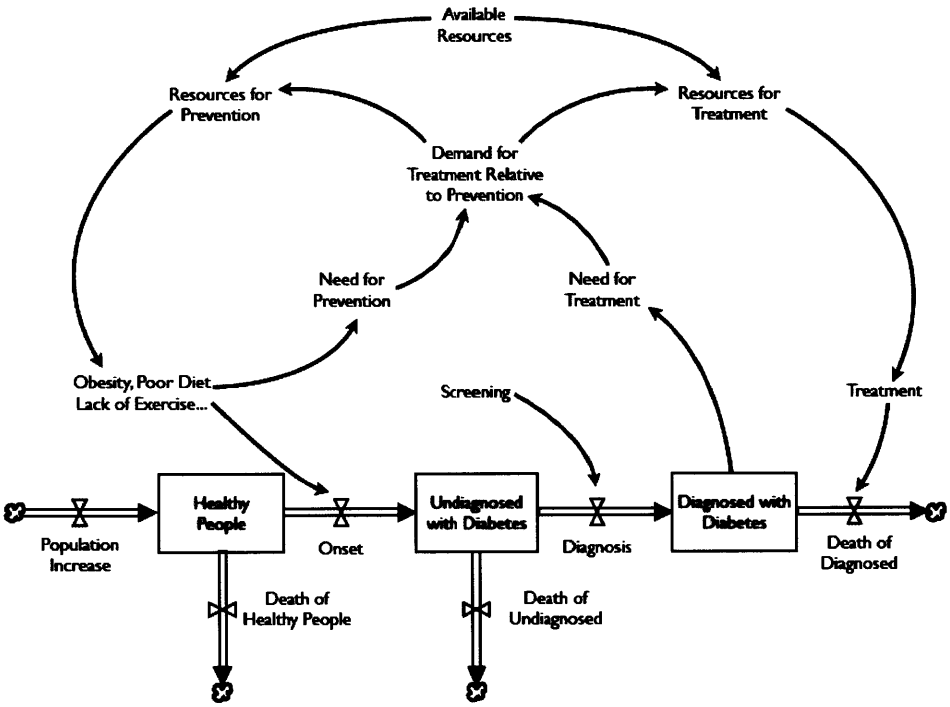


Figure 2-2 Diabetes Prevention Versus Treatment System Dynamics Model (18)

The need for urgent treatment resources is typically more visible than long-term effects of lack of prevention, resulting in more resources towards the treatment. Also, insurance incentives have historically been arranged to pay for treatment but not necessarily preventative measures.

Ornish details the dynamics in *Newsweek*, *"[In 2007,] 95 cents of every medical-care dollar went to treat disease after it had already occurred. At least 75 percent of these costs were spent on treating chronic diseases such as heart disease and diabetes that are preventable or even reversible. [...] For example, insurance companies pay more than $30,000 to amputate a diabetic foot even though most amputations are preventable by scrupulous foot care, which is usually not covered by insurance."*(19)

More recently, some corporations have redeveloped health care plans to pay 100% of preventative care and shown results of lower overall costs (19). Vaccines are an important preventative medicine and the impact of shift towards preventative measures will impact demand and capacity requirements in manufacturing.

2.2. Vaccine Industry

2.2.1. Purpose of Vaccines

Vaccines are an immunization that contains weakened or dead organisms that create immunity in the body against diseases without introducing the disease. The utilization of vaccines has eradicated smallpox and near-eliminated polio and prevented significant quantities of death and suffering across the world (20).

2.2.2. Types of Vaccines

There are four main types of vaccines, categorized as 'live attenuated', 'killed', 'purified subunit', and 'recombinant subunit' (21). Vaccines can be described with the number of valencies, such as monovalent, bivalent, and trivalent. Some vaccines are made with egg-derived manufacturing processes and others use cell-culture technology with mammalian, yeast, or other cell lines (21). Vaccines can be produced with an *adjuvant*, which requires less antigen per dose by increasing the immune system's reaction to the vaccine (1). Use of an adjuvant is not allowed by all regulatory agencies for regular use, but is maintained as a feasible option during a pandemic to quickly increase available supply.

2.2.3. Regulatory Dynamics

Regulatory agencies place increased emphasis and inspections on vaccine manufacturing facilities because products are used by healthy patients and a large percentage of the population, compared to treatment-related pharmaceutical products that are used by illness-inflicted patients. As Chiron itself learned in 2004, a failed regulatory inspection can have significant damaging

effects on reputation and financial valuation (22). Regulatory concerns for Chiron allowed for an opportunity for acquisition by Novartis (23).

2.2.4. Anti-Vaccine Movement

Since the inception of vaccines, there has been opposition to the use of vaccines (24). The most recent anti-vaccine movement began in 1998 when Dr. Andrew Wakefield wrote an article linking the MMR vaccine to autism (25). Since, the article has been retracted and discredited, while US cases of measles increased by seven times beyond historical levels (26). Described by Hofstadter in 1964, the movement of a minority towards anti-intellectualism can have lasting effects for decades (27). The anti-vaccine movement has decreased demand, increased variability, and impacted manufacturing capacity management.

2.2.5. Demand with Epidemics

Vaccines can be used for prevention in advance or as an immediate precaution in an area of an epidemic, such as an outbreak of meningitis. This is similar to the dynamics shown in Figure 2-2; in this instance, a given product can be used either for prevention or immediate reaction to a threat which impacts demand. The Department of Health and Human Services, as other regulatory agencies, has developed a process for authorizing emergency use of vaccines during an epidemic; this includes using an unapproved product or a product not approved for a given use (28).

2.2.6. Herd Immunity

The effectiveness of vaccines in the protection of the general public population is proportional to the percentage of people who are vaccinated. As shown in a system dynamics diagram in Figure 2-3, the flow of disease is affected by the carriers and population of immunized people.

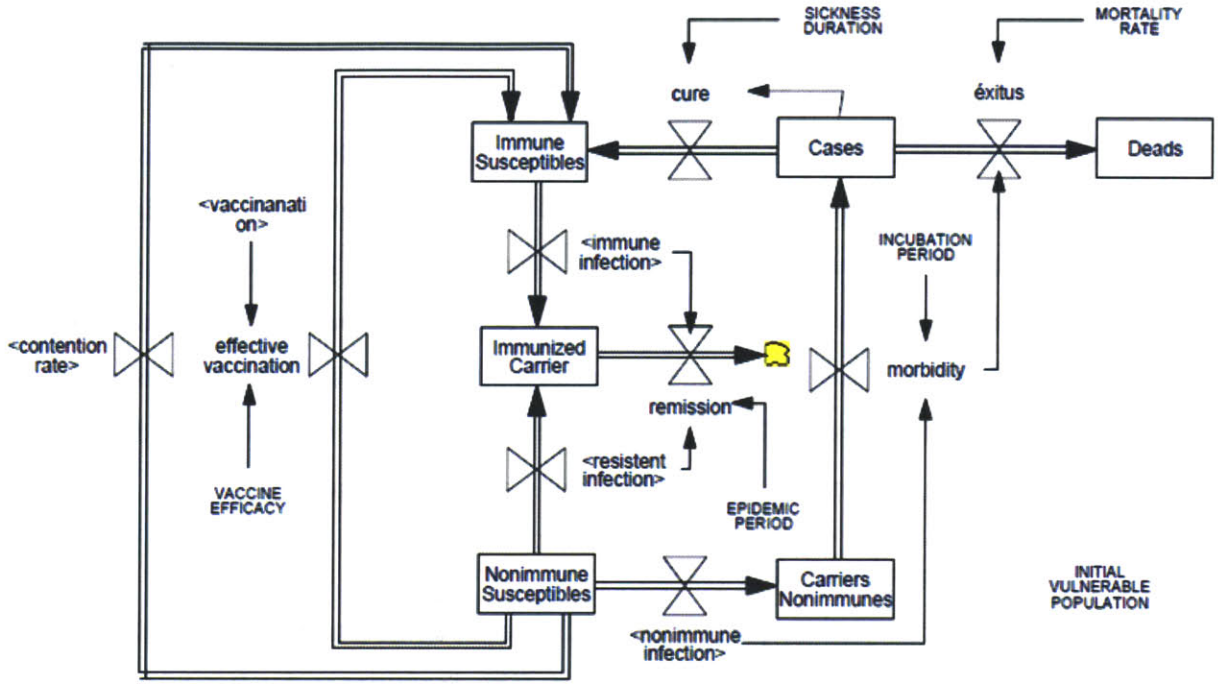


Figure 2-3 Infection Flow as System Dynamics Model (29)

As shown by Sterman, the level of the susceptible population dictates the likelihood of an outbreak (17). Sufficiently immunizing the population to above the herd immunity threshold will significantly reduce the number of future cases of the disease (24). In Figure 2-5, the response graph shows how the dynamic between the positive and negative loop reinforcing structure fight at the tipping point towards epidemic versus controlled outbreak.

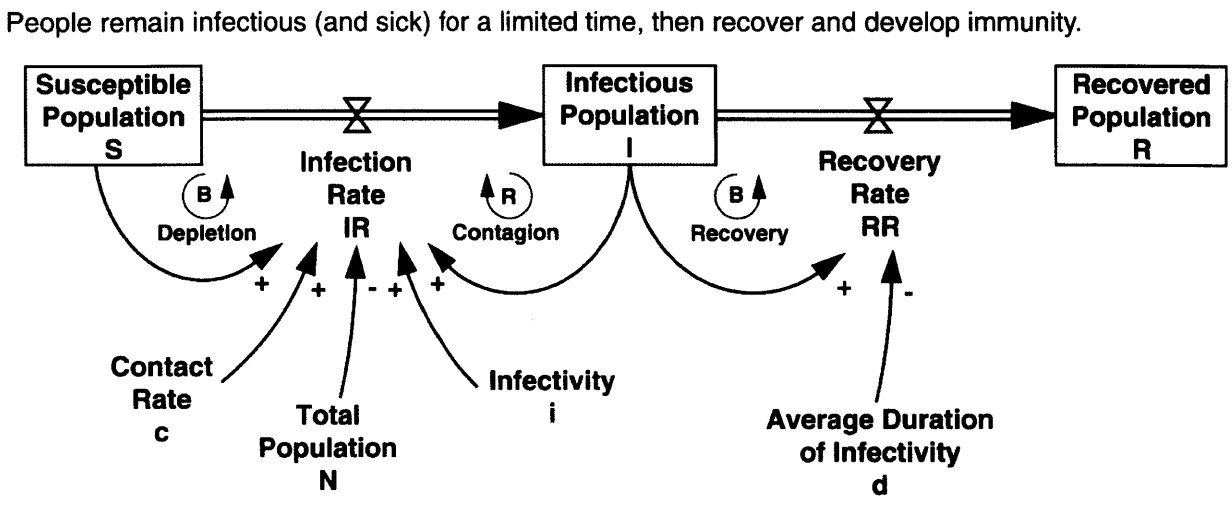


Figure 2-4 Epidemic Infection System Dynamics Model (17)

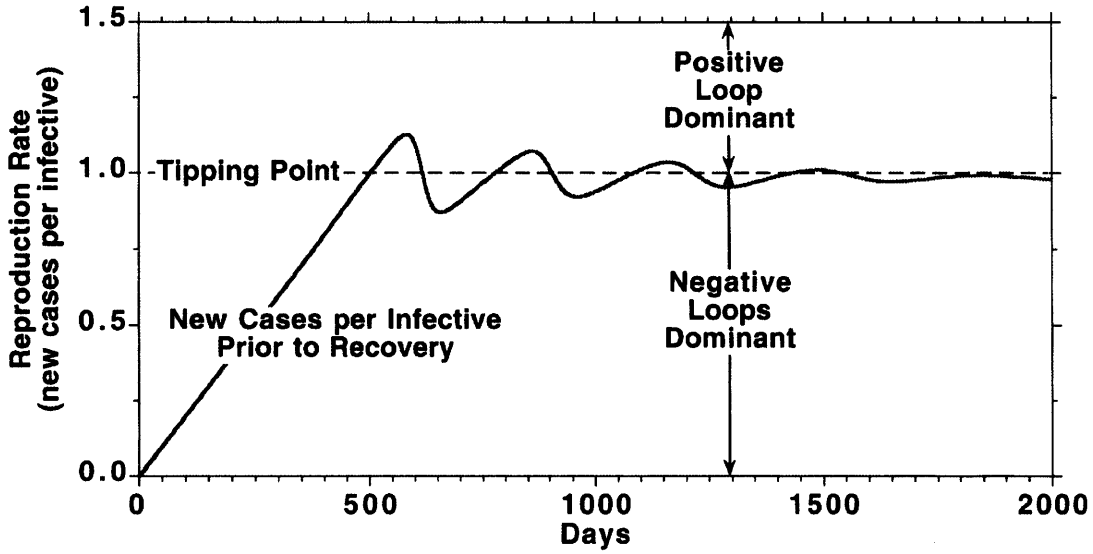


Figure 2-5 Tipping Point Loop Dominance Structure of an Epidemic Infection (17)

After a longer duration, the herd immunity may decrease as members discount the need for vaccination (due to lack of prevalence of disease or anti-vaccination concerns) and the incidence of infection can rise, as has occurred with measles in the United Kingdom after 1997

with drop below the threshold (30). The WHO recommends a vaccination rate of 95% to develop herd immunity (30).

2.3. Company - Novartis

The dynamics of the industry has lead to more acquisitions of biotechnology, including the 1996 merger of Ciba Geigy AG and Sandoz AG, to create Novartis AG (12). Novartis is headquartered in Basel, Switzerland with 120,000 employees in approximately 140 countries worldwide as of 2010. Novartis has a mission to "discover, develop, and successfully market innovative products" (31). The business is divided into four divisions, Pharmaceutical, Consumer Health, Vaccines and Diagnostics, and Sandoz (generic pharmaceuticals). In 2010, the net sales of Novartis totaled over US$50 billion (32), and Novartis ranked most innovative pharmaceutical company by Forbes Magazine in 2011 (33).

2.4. Novartis Vaccines Division

2.4.1. Formation of Division

The Vaccines and Diagnostics division of Novartis was formed in 2006 with the acquisition of Chiron for $5.4 billion (23). The US headquartered division is led from Cambridge, Massachusetts, with the Technical Operations leadership in Holly Springs, North Carolina. Key sites and personnel are also in Marburg, Germany; Siena and nearby Rosia, Italy; Liverpool, England; and former Chiron headquarters of Emeryville, California. Upon transition, many key leadership of Chiron were replaced, and people were brought to Novartis from other companies to lead the division (23).

The Novartis Vaccines facility in Holly Springs, North Carolina was developed with $486 million investment from the Department of Health and Human Services of the United States government for pandemic response capability (34). Additionally, the 2009-10 H1N1 flu pandemic impacted the company and the financial position of the division. The added financial

liquidity allowed for further development of the facility capabilities and strong growth of the division, including growth and development of the Rosia location.

2.4.1. Key Products

Novartis Vaccines and Diagnostics division focuses on providing more than 20 vaccines to fight disease and creating diagnostic instruments and testing equipment (31). Vaccine products include five types of meningococcal types, influenza, rabies, and encephalitis. A pipeline of new vaccine products are in development, including streptococcus, HIV, and respiratory syncytial virus, and more types or line extensions for meningococcal and influenza (35). Both meningococcus and haemophilus influenza B are a *purified subunit* type of vaccine made from polysaccharides, and Fluvirin is grown in eggs using a live attenuated virus (21).

2.4.1. Meningitis

Novartis Vaccines produce several types of meningococcus products. Menveo is for meningococcal groups A, C, W-135, and Y, approved for use in the US by the FDA in February 2010. Menveo continues to gain regulatory approval worldwide and recommendation for use by agencies, including a committee from the Center for Disease Control (36). Menveo is an oligosaccharide diphtheria CRM197 conjugate vaccine; the CRM197 intermediate is also produced by Novartis.

Figure 2-6 Menveo Logo (35)

Novartis Vaccines also produces Menjugate, for meningococcal group C only. Meningococcal group B is becoming more prevalent, particularly in Europe and New Zealand. MenB is a much more difficult to develop vaccine, because of only a limited immune system reaction. Currently Novartis Vaccines offers MenB vaccine for New Zealand and is developing more vaccines for increased coverage of the five main serotypes (A, B, C, W-135, and Y) (37).

2.4.2. Influenza

Fluvirin, haemophilus influenzae type B, and other flu products have been crucial to the livelihood of Novartis Vaccines. The revenue from the 2009 flu pandemic continues to benefit the division.

After identification of a flu strain, it takes five to six months to produce supplies of approved vaccine (38). Rosia Bacterial Operations do not make any seasonal flu products, but the production of seasonal flu vaccines impact the processing because of shared resources for secondary production and supply chain.

2.5. Siena/Rosia Site and Dynamics

The Italian representation of Novartis Vaccines and Diagnostics is centered in Siena, Italy, and Rosia, a small town about a half-hour drive from Siena in the Tuscan region. The Sienese presence in vaccine manufacturing was started by Achille Sclavo, an innovator in hygiene and vaccines (39). His presence is still prominent with a street and many buildings named for his work.

The Siena site is strongly focused on research and development and a strong base for administrative resources. In Rosia, the manufacturing-focused site contains many steps in the value chain process, including bulk manufacturing, secondary or parenteral manufacturing, packaging, and distribution.

Upon transition of Novartis leadership, many of the original personnel still remain and some personnel have operated in the same position for many years. In the recent years, plant management has added leadership from NVD headquarters or other international pharmaceutical and biotech manufacturers. Operational changes were made to improve operational efficiencies, such as extending some operating facility hours to 24 hours a day for five, six, or seven days a week. The organization was restructured near the beginning of this research project to be product-focused rather than aligned with the areas of the plant. This aligns with the principles in *Lean Thinking* to align the organization with business goals (40).

2.5.1. Facility – Bacterial Operations in Rosia, Italy

This research-based thesis project is focused on the Bacterial Operations in Rosia, Italy and relating components throughout the value chain of vaccines. Primary products of the facility include intermediates for Menveo, Menjugate, and Hib vaccines.

3. Project Approach and Methodology

3.1. Overview

This facility, like many, has many opportunities for operational improvement. During several conversations with plant leadership, many opportunities for improvement were identified.

Questions from Facility Leadership for Project Scoping

- How can the facility be used to launch new products? What resources are needed? Which products are a good fit in the facility and which should be ran in another facility or at a third party?
- What is the maximum facility capacity, and what are the theoretical bottlenecks?
- How should the long-range schedule be designed to optimally campaign products?
- Which projects should be prioritized to give most value for capital and personnel resources?
- How much inventory should be held of intermediate and final products?
- What opportunities are available for cycle time reduction?
- What operational improvement ideas can improve facility capacity?

3.2. Project Scope

Following these discussions with management, the project was focused on three areas.

- Model and analyze capacity, evaluate various production scenarios
- Determine theoretical bottlenecks and facility constraints
- Review product changeover frequency, inventory placement for long-range schedule planning

Three techniques were used to answer the questions proposed by management.

- Capacity analysis through process modeling
- System optimization for long-range schedule improvements
- Supply chain calculations for campaign planning and strategic inventory review

3.3. Impact to Production Decisions System

The project interfaces and has impact to many parts of the decision making chain for manufacturing as shown in Figure 3-1. Strong interfaces with strategic long-range planning are to understand the questions which need to be answered by the capacity modeling for the facility. Demand management is an input to the supply chain calculations to understand the amount of material that is necessary to produce. Operational improvements at the site can be focused on areas with highest level of impact. Material planning analytically reviews safety stock and desired inventory levels to ensure customer service. Master production scheduling and strategy impact the capacity of the facility and utilization strategy, balancing personnel resource allocation with physical assets.

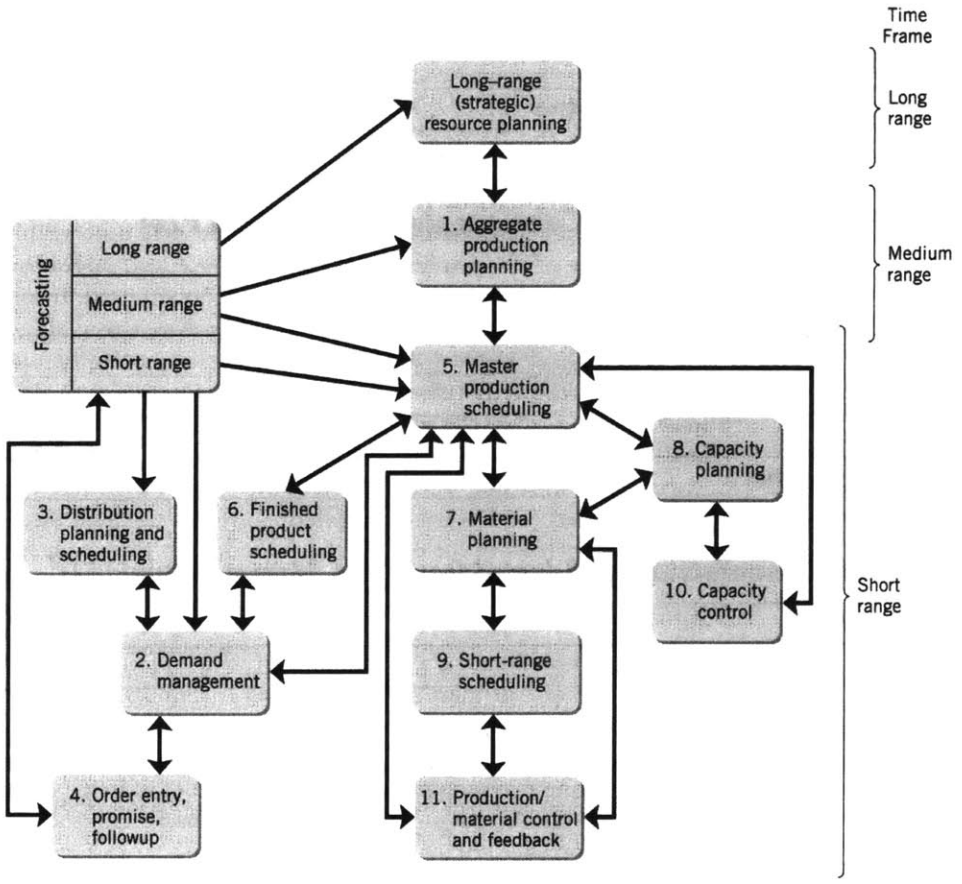


Figure 3-1 Production Decision Making Framework (41)

3.4. Facility Overview

As described in a release by the FDA, the process for Menveo includes the following production areas, general manufacturing steps, and key equipment and utilities.

Table 3-1 Menveo Production Overview *(Adapted from FDA Memorandum)* (42)

• Antigen Manufacturing
• MenCWY Formulation, Filling, Inspection of vial
• MenA Filling and Lyophilization of vial
• MenA and MenCWY Inspection, Labeling, and Packaging
• Warehouse, Storage, and Raw Materials

Table 3-2 Manufacturing Steps of Menveo Antigen *(Adapted from FDA Memorandum)* (42)

• CRM197 Manufacturing
• Polysaccharide Manufacturing
• Oligosaccharide-CRM Bulk Manufacturing

Table 3-3 Manufacturing Equipment Components *(Adapted from FDA Memorandum)* (42)[1]

• Tanks
• Columns
• Centrifuges
• Autoclave
• Parts and glassware washer

Table 3-4 Utilities in Manufacturing *(Adapted from FDA Memorandum)* (42)[2]

• Purified Water (PW)
• Water for Injection (WFI)
• Clean Steam (CS)
• HVAC

[1] Example data for illustrative purposes
[2] Example data for illustrative purposes

3.5. Variable Definitions

The following tables describe the input variables, output calculations, decision variables, and constraints used across the process modeling, system optimization, and supply chain calculations.

3.5.1. Input Variables

Many parameters and data are available from processing information to utilize in this analysis. Table 3-5 lists input variables considered for this research.

Table 3-5 Input Variables

Variable	Title	Description	Units	Example Values
j	Job	Bulk products produced, or intermediates for final products	Text	Conjugated MenA
i	Machine	List of equipment units or production area	Text	Column, tank, autoclave
p	Product	Final product for which intermediate is used	Text	Menveo, Menjugate, Hib
a	Processing Area	Area of plant; used to meet cross contamination constraint	Text	Fermentation, Purification
s_{SOP}	Processing step number	Processing step of the plant, by SOP number	Numerical	SOP 111111
m	Material name	Material used during production; Raw material, utility, buffer, consumable or other material used during production step.	Text	WFI, CS, PW, column resin
x_{js}^{i}	Binary machine use	Binary variable for if the machine is used for a given job in a given step $\equiv$ 1 if machine is used for job j in step s, else 0	Binary	1 or 0
x_{js}^{a}	Binary processing area	Binary variable for if the processing area is used for a given job in a given step $\equiv$ 1 if processing area is used for job j in step s, else 0	Binary	1 or 0

Variable	Title	Description	Units	Example Values
d_j	Due date	Date that job j is to be completed	Time	March 23
P_{ij}	Processing time	Processing time of job j on machine i	Duration	2.34 hours
$h_{ij_nj_{n+1}}^{change}$	Sequence-dependent changeover time	The duration of time to switch from job j_n to job j_{n+1} on machine i If the same job is run sequentially on the same machine, the set up time is defined as zero $h_{ij_nj_n}^{change} \equiv 0$	Duration	0.3 hours
R_{jp}	Recipe	Recipe for producing one mds of product p requires R_{jp} grams of job j	Grams/ Million doses (mds)	5 grams/mds MenC-CRM (43)
D_p	Demand	Demand for product p (typically annual)	Million doses (mds)	10 mds
g_j	Grams per batch	Bulk grams of job j produced, at antigen production outlet	Grams/ batch	4 g/batch of MenC-CRM[3]
G_j	Grams in inventory	Total bulk grams of job j $G_{j_0} \equiv$ grams of initial inventory of job j	Grams	10 g
G_j^{tgt}	Target grams in inventory	Total target bulk grams of job j	Grams	20 g of MenC-CRM
Y_{js} or Y_{ij}	Yield	Yield of job j in step s or machine i	%	95%
U_{ijm}^{mtl}	Utilization of material	Utilization of material m in machine i for job j	Units of material	5 liters of Raw Material
W_a	Workforce	Workforce authorized for processing area a	Dimensionless quantity	8

[3] Example for illustrative purposes, not actual data

Variable	Title	Description	Units	Example Values
$c_{i\,j_{n-1}j_n}^{setup}$	Changeover costs	Setup costs for changing from job j_{n-1} to job j_n on machine i If the same job is run sequentially on the same machine, the set up costs are defined as zero $when\ n-1=n;\ c_{i\,j_{n-1}j_n}^{setup} \equiv 0$	€	€10,000

3.5.2. Output Calculations

Output calculations are values dependent on input parameters and optimization function.

Table 3-6 Output Parameters

Variable	Title	Description	Units	Equation
G_j	Grams produced	Bulk grams of job j available (produced or in inventory)	Grams	$G_j = g_j \times L_j + G_{j_0}$ $\forall\ (j)$
C_{ij}	Completion time	Completion time of job j on machine i	Time	$C_{ij} = y_{ij} + P_{ij} + t_{ij_{n-1}j_n}^{change} + th_{ij}^{clean}$ $\forall\ (i,j)$
C_{max}	Makespan, Maximum completion time	Defined as the duration of time until the last job leaves the system	Duration	$C_{max} = \max(C_j)$ $\forall(j)$

3.5.3. Decision Variables

The decision variables are the parameters which are variable and are determined by calculation of optimal values.

Table 3-7 Decision Variables

Variable	Title	Description	Units
L_j	Lots	Lots or batches produced of job j	Dimensionless
y_{ij}	Starting time	Starting time of job j on machine i	Time

3.5.4. Process Constraints

The process constraint equations represent the physical constraints mathematically for data analysis. The constraints in the pharmaceutical industry are different than many other industries, due to high regulation from worldwide agencies and cross-product contamination.

Table 3-8 Process Constraints

Equations	Description
$y_{i_{n+1}j} \geq y_{i_nj} + P_{i_nj}$ $\forall(i_n, j)$	The starting time of the next machine for a given job, $y_{i_{n+1}j}$, must be later than the sum of the • starting time of the previous machine for a given job, y_{i_nj} • processing duration of the previous machine for the given job, P_{i_nj} • time to change equipment between jobs, $t^{change}_{ij_nj_{n+1}}$ • time to clean between jobs, t^{clean}_{ij}
$y_{ij_{n+1}} \geq y_{ij_n} + P_{ij_n}$ $\forall(i, j_n)$	The starting time of the next job for a given machine, $y_{ij_{n+1}}$, must be later than the starting time of the previous job for a given machine, y_{ij_n}, plus the processing duration of the previous job on the given machine, P_{ij_n}.
$C_{max} \geq P_{ij} + y_{ij}$ $\forall(i,j)$	The duration of time to complete all jobs, C_{max}, must be greater than or equal to the time to complete all jobs. Does not include cleaning and changeover after final job. Cleaning and changeover are not included because they are before the start of the step.
$G_j \geq D_p \times R_{jp}$ $\forall(j,p)$	The total number of grams available of job j must be greater than or equal of the amount of grams needed to fulfill demand D_p.
$\forall(a,y), \sum_{j=0}^{j} x^a_{js} \leq 1$	For all production areas a, the sum of the number of jobs j in a given production area a at any given production time, y, must be less than or equal to one to prevent cross contamination.
$\forall(i,y), \sum_{j=0}^{j} x^i_{js} \leq 1$	For all machines i, the sum of the number of jobs j active at any given production time, y, must be less than or equal to one.
$L_j \geq 0$ $\forall(j)$	Non-negativity of number of lots produced
$y_{ij} \geq 0$ $\forall(i,j)$	Non-negativity of starting time
$P_{i_{n+1}j} \geq P_{i_nj}$	Precedence of previous jobs

4. Capacity Modeling and Simulation

4.1. Capacity Analysis and Theory

Capacity analysis in biopharmaceutical manufacturing has historically been focused on single-product facilities. With the development of more specialized products and fewer blockbusters, the industry has trended to more multi-product facilities for active ingredient production.

With demand and approval uncertainties and a long lead time to build and qualify a new facility, capacity decisions are difficult in the pharmaceutical industry. The high margins in pharmaceutical industry, which apply to most non-commodity products, establish that the financially best option is to have enough capacity to meet virtually all demand, as shown in Equation 4-1.

Equation 4-1 Cost of Exceeding or Under Producing Demand (44)

$$area\ under\ demand\ curve = \frac{C_u}{(C_o + C_u)}$$

$$C_u\ Cost\ of\ Underage\ of\ Production\ Units$$

$$C_o\ Opportunity\ Cost\ of\ Overage$$

In the pharmaceutical industry, the cost of underage, or shorting the market, often involves additional negative effects other than the loss of a sale. For specialized products, market backlash can include loss of reputation for other products, reduced confidence in future ability to deliver, and accelerated regulatory approval of competitor products. Third-party manufacturing options allow for delaying or hedging of capacity decisions with uncertain demand, and can aggregate capacity across the industry and lower overall risk (45) (44).

For additional review of capacity theories, refer to Sterman, *Business Dynamics* (17); Beckman and Rosenfield, *Operations Strategy* (44); Silva, *Capacity Management: Get the level of detail right* (46); and Pinedo, *Scheduling* (47).

4.2. Defining Capacity

For this project, capacity is defined as physical capacity limited by the fixed equipment in the facility. Disposable or readily available commodities (e.g., lab glassware, storage containers, disposable bioreactor and liquid storage bags) are assumed to be readily available and non-constraining to the capacity.

In contrast, a facility capacity can also be defined by a limited headcount to operate, support, and manage the given equipment resources. Similarly, the model will exclude personnel constraints but consider level scheduling benefits when considering non-capacity constrained situations.

4.3. Approach

Several facility capacity models had been previously made, but were no longer in use. For this project, an essential part before commencement of the modeling project, was evaluating the key shortcomings of previous models and understanding how to develop a model that will be effectively used to provide value for several years of production.

Table 4-1 Model Development Decision Factors

1. Model capabilities
2. Audience
3. Access to model and software
4. Ease of use
5. Understanding model
6. One-time project versus multi-use model
7. Projected value of model data
8. Level of detail and preciseness required
9. Data availability
10. Integration with other systems

4.3.1. Model Capabilities

Interviews with stakeholders across plant management, technical planners, and manufacturing strategy are used to understand categorization of essential, valuable, and non-essential information for model.

4.3.2. Audience

A model is designed differently for different audiences. For example, a model built for a few technical users only on a yearly basis is designed differently from a model for use by operations personnel for weekly use.

4.3.3. Access to Model and Software

The audience dictates also the level of access needed for the model. Specialized modeling software often has restricted licensing for only a limited number of workstations. A model that is needed for use by many will be more easily accessed with a commonly used tool such as a web-based application or software that is licensed by all computers on-site (e.g. Microsoft Excel).

However, off-the-shelf software has many advantages. Software packages are available that specialize in many areas and after initial training, software tools have templates, reports, and graphs that make development and use more rapid.

4.3.4. Ease of Use

Ease of use of the model is important particularly if the model will be used by a large audience on a regular basis. A user interface is important to quickly display key parameters and visually show metrics. However, simplicity and ease of use is often in contrast to model capabilities and the ability to update model. For models that will be only designed by one or two people with low risk of personnel change, models requiring many days of specialized training may be feasible; expensive training for many on a simpler model does not drive value.

4.3.5. Understanding Model

A dashboard quickly summarizing key value parameters or a report summarizing recommendations transforms models into organizational value. Subsequently updating the model to reflect new capabilities after facility changes or to test new product integration over time will require need for shared learning and understanding of the model. Consideration for use of a training document or other means for communication may be valuable to the organization.

4.3.6. One-time Project Versus Multi-use Model

The expected utilization drives the functionality and flexibility. If the model needs to be flexible to allow for new product introductions and facility changes, simplicity in structure and a detailed user's guide are valued additions. For a single-use project, more value is gained by developing a tool quickly and extracting the value in a report.

4.3.7. Projected Value of Model Data

The projected value of the model should dictate the amount of resources dedicated to developing the model. The cost of generating the model should not be so significant that it diminishes the value of the model.

4.3.8. Level of Detail and Preciseness Required

Also related to the projected value of the model results, the level of detail in the model should be just enough to achieve the needed value of the project. As described in *Capacity Management* (46), different level of detail is needed to complete different tasks to analyze capacity.

Additional levels of specificity may be available for later expansion, but the core of the model should be built first for testing and to drive immediate value, then additions can later be added as applicable. For example, a model can be built first for one representative product or area of the facility, and then expanded to encompass the larger facility.

4.3.9. Data Availability

The accessibility, quantity, and availability of data dictate the type of model as well as the level of detail. For a new facility, or a facility in development, actual production data for cycle time and yields are not available and must be estimated from clinical trial production and estimates from industry standards. An operating facility may have significant amounts of electronic records available for data mining and many cycles of yield data for capacity estimates. However, an established, older facility may require individual data collection from future production runs or manual data gathering from historic written-only batch production records (BPR).

4.3.10. Integration with Other Systems

Many systems can extract and collect data from other computer systems, such as data historians. The ability to collect historical data for averaging and statistical analysis, and then use it to validate an initial model or update parameters of an existing model can be of high value to a business.

4.4. History of Modeling at Facility

Upon scoping and evaluating for the capacity model, discovery of several previous models occurred. However, each of these models had various faults, which led to the request for me to develop another model.

After many discussions with creators of previous models, expectations of over-confidence and defensiveness towards the existing models were not realized. Each person was quite open to discussing what they did, the information they gathered, and the limitations of their models. They were interested to help provide information to develop a sustainable model.

Upon talking to these developers of the previous models, users of the models, and plant leadership, several themes arose of faults in previous models.

Table 4-2 Common Problems in Capacity Modeling

• Random or undefined assumptions	• Inadequate restart times between batches or process shutdown times
• No incorporation of demand on utilities and waste systems	• Maintenance requirements grouped at one time versus spread out throughout year for maintenance staffing
• Assumptions on facility operations not based on theoretical capacity and analytical calculations	• Personnel staffing dynamics
• Compounding error by frequent conversions	• Poorly documented model
• Much higher or lower than historical assumptions for factory losses	• Improper handoff to new area, when new person left or if it was done by external resource
• Difficult to obtain software or licenses for widespread use of model	• Model not updated for new process changes
• Converting between grams, doses, overfill, safety stock, batches	• Modeling addition of new products into facility

Knowing weaknesses about other existing or previously developed models at a given company or factory help strengthen and develop future models to prevent recurrence of issues and deliver a model properly fit, in delivery, execution, and system, to achieve more results.

4.5. Political Dynamics of Models

Political dynamics are also important to understand when building a model. Barriers to model implementation may exist if the model is not developed with proper incorporation of stakeholders and sets of data. Implementation of model to change production operations can have significant effect on employees and the staffing schedules. Recommendations may not be popular to all groups across the facility.

Table 4-3 Political Dynamics of Models

• A model which recommends reduction in headcount or reallocation of resources may lower employee morale or be difficult to implement
• Model may show that previous projects were not necessary, such as a capacity increase project on a part of the facility that is not a true bottleneck
• Completing the model in isolation without input from the facility can result in poor acceptance of model results
• An external contractor or part-time employee may have more difficulty building credibility with team for information gathering or project implementation
• Previous failed or unused models may prompt early negativity on new models

4.6. Model Software Selection

Selecting the proper software is essential to the success and utilization of a model. Many key factors were considered in determination of the best software.

Table 4-4 Modeling Software Selection Considerations

• Software capabilities
• Software license terms (annual fee, lifetime, single station versus multiple user installations)
• Current company usage
• Industry usage
• Long-term support of software at company
• Speed of acquisition
• Cost

When selecting modeling software, leveraging resources can help evaluate software options. At Novartis, a social media tool named Yammer (48) was used to collaborate and share modeling software ideas and user information. Typically, this knowledge sharing across a corporation with over 100,000 worldwide employees would have been significantly more difficult. With Yammer, this knowledge gathering was done passively with opt-in only by people who were interested to share knowledge or gain collaborative information. Other resources that are valuable for software evaluation are in Table 4-5.

Table 4-5 Resources for Software Evaluation

• Software vendors
• Company information technology (IT) group
• Internal technical resources and documentation
• Fellow students or PhD students
• Internet resources
• Resources to build a user-interface for a more complicated tool

Many software packages were recommended and evaluated for this project; refer to Table 10-1 for a list of software. For a detailed comparison between Aspen Plus and SuperPro for use in vaccine manufacturing, refer to Shanklin et. al., *Selection of Bioprocess Simulation Software for Industrial Applications* (49).

4.7. Bacterial Operations Modeling Selection

Aspen Batch Process Developer (formerly Aspen Batch Plus) was chosen for modeling capacity of the Novartis Bacterial Operations facility. The model is developed for use by only a few users, on a semi-annual basis. Aspen Plus is used across Novartis in several areas, and group licensing is purchased for the corporation. IT support is currently provided, but in-house knowledge of software is limited in the Novartis Vaccines division. SuperPro was also identified as a suitable modeling tool but Aspen was chosen for speed of software acquisition and existing software licensure at Novartis.

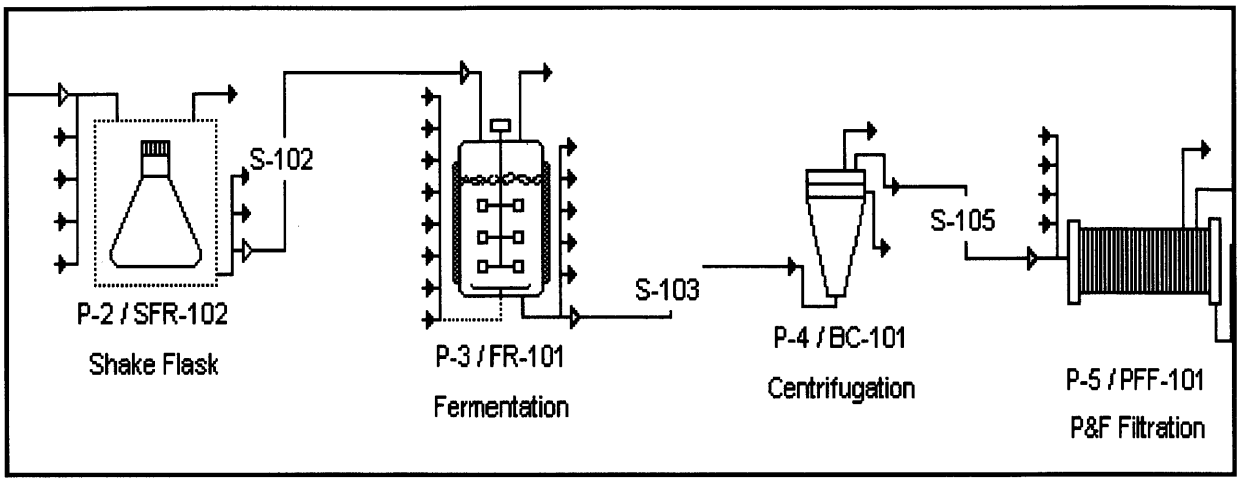


Figure 4-1 Example Process Model in SuperPro[4]

4.8. Data Collection

In parallel to evaluating modeling software, modeling data was collected. Typically, gathering data takes extra time, either for collecting real-time process data, to gain computer system access to computer systems, or for report aggregation. During project scoping, review the available data and begin collection of data for use in early models.

4.9. Model Development and Validation

The model was created in Aspen Batch Process Explorer with initial focus on the MenA process as a representative sample of production. After creation of the model, the model can be validated against actual production data or, for a new facility, industry benchmarks and trends.

4.10. Sensitivity Analysis and Simulation

One of the primary uses of the model is for simulation analysis of future products into the facility. The model can be used to evaluate fit of the new product into the facility, what additional equipment and capabilities are needed and potential impact in capacity of other

[4] Example for illustrative purposes, not actual data

products. As the model is used for decision processing, sensitivity analysis should be completed around the process bottlenecks and assumptions.

4.11. Model Implementation and Recommendations

For next steps, the model can be replicated for other intermediate products, and detail addition for utilities and headcount. As facility constraints are tested for new product integration, the model can be replicated for introduction and facility fit. Additionally, this model was built with the intent of limited users with trained knowledge of the tool. Appropriate resources will need to maintain training and update tool to reflect facility changes.

4.11.1. Exploratory Stress

Exploratory testing is recommended to test and constrain different operating conditions in a controlled environment before the facility is fully utilized. This model can be used to identify scenarios of potential weakness in the operations to then test in the production environment in a controlled test.

Stress testing is a valuable tool for testing a system and is common for software platforms. As described by Microsoft, *"Stress testing* is a type of performance testing focused on determining an application's robustness, availability, and reliability under extreme conditions. The goal of stress testing is to identify application issues that arise or become apparent only under extreme conditions." (50)

An analogy of a sea filled with many icebergs is used to visualize the increasing stress on the system. Icebergs have various peaks, some of which rise above the water surface and some are fully submerged, but each peak remains a potential hazard to a ship. As the water level decreases, more and more icebergs become visible to the surface.

Similarly, a manufacturing is described as having various underlying issues, invisible to the eye, but under different circumstances, can arise and cause a disruption to operations. Intentionally lowering the water, or creating *exploratory stress* on the system, can produce new ideas and identify unknown weaknesses in systems. After identifying these weaknesses of the

system, they can be mitigated and resolved under a controlled environment rather than in an unplanned or emergency situation.

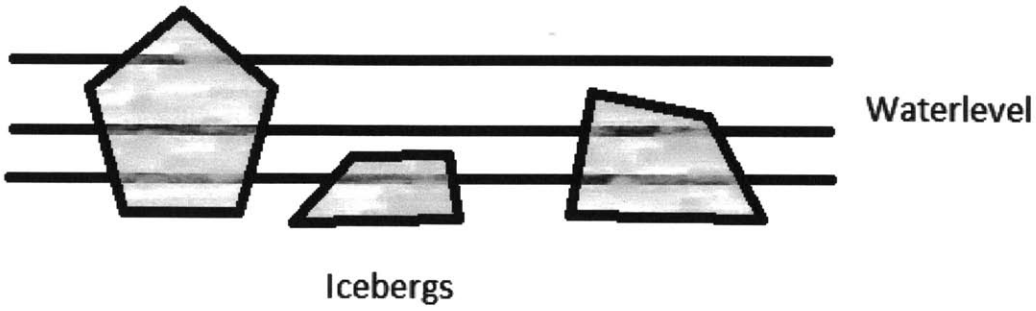


Figure 4-2 Icebergs of Danger . . . or Opportunity

In *The Toyota Way*, a scenario is described with use of the *kanban* system to integrate improvements. A system is currently operating with four *kanban* with production parts in manufacturing. If one *kanban* is removed from the system, the process can be analyzed to stress the system and determine operational improvements to the planned disruption (5).

Stress testing is common in the software industry to test peak usage or process bounds of the software product for improvements (50). Figure 4-3 and Table 4-6, as developed by Meier, et.al., detail a technique for Stress Testing.

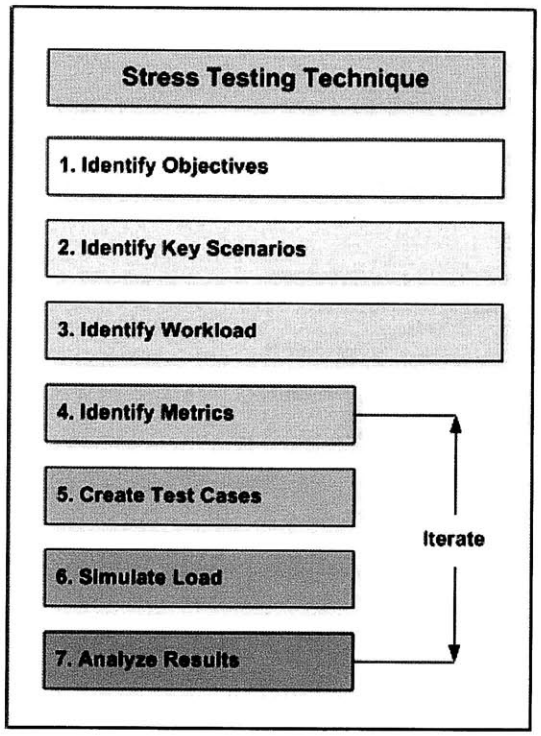


Figure 4-3 Stress Testing Process ***(as presented by Meier, et.al.)*** **(50)**

Table 4-6 Detailed Stress Testing Parameters ***(adapted from Meier, et.al.)*** **(50)**

Step	Objective
1	Identify test objectives. Identify the objectives of stress testing in terms of the desired outcomes of the testing activity
2	Identify key scenario(s). Identify the application scenario or cases that need to be stress
3	Identify the workload. Identify the workload that you want to apply to the scenarios identified during the "Identify objectives" step. This is based on the workload and peak load capacity inputs.
4	Identify metrics. Identify the metrics that you want to collect about the application's performance. Base these metrics on the potential problems identified for the scenarios you identified during the "Identify objectives" step.
5	Create test cases. Create the test cases in which you define steps for running a single test, as well as your expected results.
6	Simulate load. Use test tools to simulate the required load for each test case and capture the metric data results.
7	Analyze results. Analyze the metric data captured during the test (50).

Currently, the Bacterial Operations facility at Novartis has excess capacity. The facility would be strengthened by testing this idea in production. A few scenarios of that can be tested in the facility are as follows.

- Cycle time for theoretical bottleneck steps
- Product changeover
- Utilities, including water and key waste tanks
- Buffer storage – limit number of available racks for buffer storage to lower buffer inventory and improve storage arrangement
- Operators for given production area

Additionally, historical and cultural operational biases limit the perceived capabilities of production. As described in Section 2.4, many changes were made after facility acquisition by Novartis. Presenting the idea of looking for weaknesses in the facility operations can continue the development of a culture of continuous improvement and idea generation.

5. Cycle Time Optimization

5.1. Introduction

Within the model creation, an additional focus arose to look for opportunities for cycle time reduction. To complete this, a system optimization model was created using minimum time inputs and processing constraints. Then, the optimization is compared to the actual production to seek cycle time improvements.

In the future, when the production needs are greater and the facility may be capacity constrained, minimizing cycle time will be a need. However, the equipment is currently not capacity constrained, and the needs now are towards leveling resources and operational headcount needs.

5.2. Optimization Model Project Plan

Jérémie Gallien, as presented in System Optimization course 15.066 at MIT in the summer semester of 2009, has developed a set of steps for approaching a system optimization project (51). In whole, the approach is iterative to sequentially gather data and build parts of the model while regularly completing validation steps and collecting feedback to improve the model and prevent rework.

Table 5-1 Modeling Project Plan Steps (51)

1. Define quantitative questions motivating simulation study
2. Get feedback
3. Define model on paper
4. Get feedback
5. Rough input data collection
6. Choose simulation software
7. Implement model on computer
8. Output data collection
9. Validation experiment
10. Perform sensitivity analysis
11. Get feedback
12. Extensive data collection
13. Validation experiment
14. Design and analyze simulation experiments
15. Summarize and communicate results

5.3. Schedule Optimization Use in Biotechnology Manufacturing

Historically, biotech facilities were built as single-product facilities where schedule planning was simpler and often done without analytical optimization tools. As more products are approved for development in multi-product facilities, the risk for manufacturers becomes lower as capital-intensive facilities are more flexible to a suite of related products, such as a family of vaccines or types of monoclonal antibodies. Mathematical modeling for biotech facility scheduling is gradually increasing in use as complex constraints and expensive cost of changeover dictate schedule dynamics (52). Multi-use facilities and schedule improvements to gain capacity from current assets are a significant opportunity to reduce overall costs of manufacturing.

5.4. Cycle Time Analysis

The system optimization is set up with ideas drawn from a value stream, where the key principles are modeled to focus on the value-added tasks in the facility. Similar to a time value map in Value Stream Mapping concepts, the schedule optimization will be used to compare minimum value-added time to how time is used during processing (53).

As described by George and Rowlands, "Of all the dozens or hundreds of actions you and your coworkers perform in your process, only a few of them make a real difference to your customer," (53).

5.4.1. Problem Setup Using Triplet Terminology

In *Scheduling* (47), Pinedo introduces a terminology to classify the type of environment used in an optimization function.

Table 5-2 Triplet Terminology *(as adapted from Pinedo)* (47)

$\propto \mid \beta \mid \gamma$	Description	Number of Entries
$\propto$	Machine environment	One entry
β	Processing characteristics	Zero to multiple entries
γ	Objective to be minimized	One entry, typically

The first parameter is to describe the machine environment. For the facility modeled, this is a job shop with a predetermined route. This is typical of bulk pharmaceutical manufacturing as a set process is developed and bound within regulatory documents. Minor choices are available if identical multi-train options are used for a process.

Processing characteristics represent the second parameter. This field can have multiple entries, but may also have none. For the Novartis facility, *recirculation* is used, as a given machine or equipment unit is used for more than one step of the process. *Precedence* is used to account for the limited hold times for product between steps, and to require that a given job, or batch, is completed prior to a subsequent or lower priority job. Within the several products made in the facility, the changeover times vary dependent on if the next product is the same or different from the previously manufactured product, so *sequence dependent setup times between jobs* is a processing characteristic. The facility is designed to have a few weeks of annual shutdown for maintenance and projects, and occasionally has unexpected downtime. This processing dynamic is represented by the characteristic *breakdown.*

The objective of the function is to minimize the total makespan for facility utilization and capacity analysis.

The triplet terminology as built for the facility optimization function is summarized in Table 5-3 Scheduling Triplet Terminology.

Table 5-3 Scheduling Triplet Terminology

Category	Category	Parameter	Description
$\propto$	Machine environment	J_i	Job shop with predetermined route to follow
β	Processing characteristics and constraints	$rcrc$	Recirculation where job may need to visit a given machine more than once
β		$prec$	Precedence constraints requiring a given job to be completed first
β		$S_{ij_{n-1}j_n}$	Sequence dependent setup times between jobs
β		$brkdwn$	Breakdown times when machines are not available (planned or unplanned)
γ	Objective	C_{max}	Makespan for good machine utilization

5.4.2. Problem Statement

The optimization function is a model of the current Bacterial Operations plant in Rosia, with equipment, demand, inventory, personnel resources, and costs as inputs. Data produced with this model is used for capacity planning, long-range scheduling, and comparison to the current operations for identification of improvement opportunities.

5.5. Optimization Model Development

As described by Bertsimas and Freund (4), the basic steps for creating a linear optimization model are to define the decision variables, develop the objective function, and then specify constraints.

5.5.1. Decision Variables

The desired output of the optimization model is the time of completion of each step, which can then be compounded into the makespan of each job and the makespan of the set of all jobs.

Table 5-4 Decision Variables for Optimization Function

Variable	Description	Units
x_{ik}	Completion time of job j on machine i for each stage k	Time
x_j	The total makespan of each job j	Time
C_{max}	The makespan of the set of jobs	Time

5.5.2. Objective Function

The objective function is to minimize the makespan of the set, *CMax*. This identifies the minimum amount of time the set of given jobs can be completed.

5.5.3. Constraints

In Table 5-5, system and regulatory limitations are detailed as a component of the optimization bounds.

Table 5-5 System Optimization Function Constraints

Equations	Description
$y_{i_{n+1}j} \geq y_{i_nj} + P_{i_nj}$ $\forall(i_n, j)$	The starting time of the a machine for a given job, $y_{i_{n+1}j}$, must be later than the sum of the starting time of the previous machine for a given job, y_{i_nj} , and processing duration of the previous machine for the given job, P_{i_nj}
$y_{ij_{n+1}} \geq y_{ij_n} + P_{ij_n}$ $\forall(i, j_n)$	The starting time of the next job for a given machine, $y_{ij_{n+1}}$, must be later than the starting time of the previous job for a given machine, y_{ij_n} , plus the processing duration of the previous job on the given machine, P_{ij_n}
$C_{max} \geq P_{ij} + y_{ij}$ $\forall(i,j)$	The duration of time to complete all jobs, C_{max}, must be greater than or equal to the time to complete all jobs.
$\forall(a,y), \sum_{j=0}^{j} x_{js}^{a} \leq 1$	For all production areas a, the sum of the number of jobs j in a given production area a at any given production time, y, must be less than or equal to one to prevent cross contamination.
$\forall(i,y), \sum_{j=0}^{j} x_{js}^{i} \leq 1$	For all machines i, the sum of the number of jobs j active at any given production time, y, must be less than or equal to one.
$y_{ij} \geq 0$ $\forall(i,j)$	Non-negativity of starting time
$P_{i_{n+1}j} \geq P_{i_nj}$	Precedence of previous jobs

5.5.4. Model Characteristics

The model was developed to address the circular job shop scheduling with the following characteristics.

Table 5-6 System Optimization Model Characteristics

• Specified set of jobs
• Specified set of machines
• Jobs can have different number of stages
• Job routings can differ for each job
• Specified number of stages for a job
• The processing of job j for stage k

5.5.5. System Optimization Equations

Equation 5-1 Definition of Variables (54)

For given machine *i*, jobs *n* and *n+1* are processed.

X_{in} or $X_{i(n+1)}$ is the time at which job *n* or *n+1* is complete

$$Y_{n(n+1)} = 1 \; if \; n+1 \; is \; executed \; after \; n$$

$$0 \; otherwise$$

Equation 5-2 Processing Order Constraint (54)

$$If \; Y_{n(n+1)} = 1 \; then \; X_{i(n+1)} \geq X_{in} + p_{i(n+1)}$$

$$If \; Y_{n(n+1)} = 0 \; then \; X_{in} \geq X_{i(n+1)} + p_{i(n+1)}$$

$$X_{i(n+1)} \geq X_{in} + p_{i(n+1)} - M(1 - Y_{n(n+1)}) \; where \; M = 10{,}000$$

$$X_{in} \geq X_{i(n+1)} + p_{in} - MY_{n(n+1)}$$

$$Y_{n(n+1)} + Y_{n(n+1)} = 1$$

5.5.6. Model Parameters

The process was modeled with a representative 22 processing steps using 17 unique equipment units, or *machines*. Additional machines were represented in excess to account for processing steps which occur in glass vessels and other non-constraining vessels. These were not considered unique machines because the ability to acquire a new piece of equipment and its supporting instruments are not considered to be a constraint from a financial or qualification stance. To represent dynamics from multiple sequential production runs, 10 batches or *jobs* were analyzed in the optimization model.

5.5.7. Incremental Model Development

For simplicity, the model was developed in multiple steps, each adding complexity to the model and more accurately describing the manufacturing facility. Building the model in small, incremental steps allowed for testing of the model and concept at the early, less complicated stages. A significant benefit to this strategy was found that the model was built initially using a simpler code interface. GUSEK (an open source solver using GLPK, a linear programming solver for Windows) was used to create the model. The solver was also able to run much more quickly with a smaller set of parameters. The model with 10 jobs required a higher level of computing functionality. Troubleshooting on the 10 job unit would take much longer because of the time to run the model each time it is executed.

Table 5-7 Iterative Optimization Model Building

Iteration	**Number of Jobs** *j*	**Number of Machines** *i*	**Number of Steps** *s*	**Plant Area Divisions** *a*	**Job Precedence Constraint** *prec*
1.	3	9	3-4	None	Yes
2.	3	17 distinct	22	None	Yes
3.	10	17 distinct	22	None	Yes
4.	10	17 distinct	22	None	No
5.	10	17 distinct	22	4	Yes

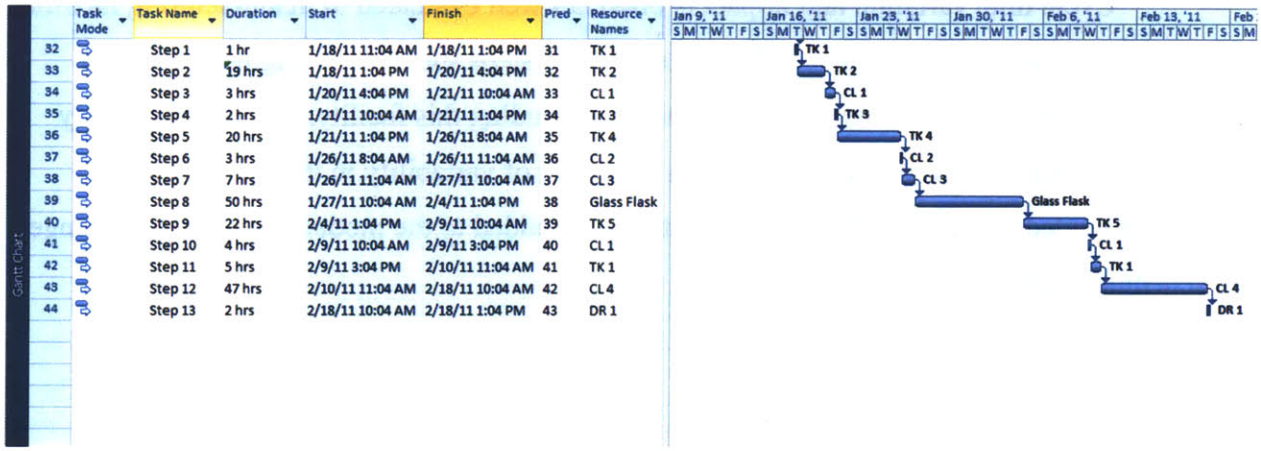
5.6. Validation

The processing times used for the system optimization function were averaged from the 2008 campaign of Men A. By using only a subset of data, the model can then be validated with other data distinct from the data used to create the model (4).

5.7. Analysis and Recommendations

The data is compared to actual cycle times, identifying areas of discrepancy and potential improvement. Process bottlenecks are identified and contrasted against other models and conventional thoughts among plant operations. A significant bottleneck was shown to be with equipment that is used for more than one step in the process and for process steps that are long durations in dedicated equipment, such as reaction steps.

Microsoft Project was used to display Gantt chart data from the optimization function. An example display of a single production batch scheduling is shown in Figure 5-1.



	Task Mode	Task Name	Duration	Start	Finish	Pred	Resource Names
32		Step 1	1 hr	1/18/11 11:04 AM	1/18/11 1:04 PM	31	TK 1
33		Step 2	19 hrs	1/18/11 1:04 PM	1/20/11 4:04 PM	32	TK 2
34		Step 3	3 hrs	1/20/11 4:04 PM	1/21/11 10:04 AM	33	CL 1
35		Step 4	2 hrs	1/21/11 10:04 AM	1/21/11 1:04 PM	34	TK 3
36		Step 5	20 hrs	1/21/11 1:04 PM	1/26/11 8:04 AM	35	TK 4
37		Step 6	3 hrs	1/26/11 8:04 AM	1/26/11 11:04 AM	36	CL 2
38		Step 7	7 hrs	1/26/11 11:04 AM	1/27/11 10:04 AM	37	CL 3
39		Step 8	50 hrs	1/27/11 10:04 AM	2/4/11 1:04 PM	38	Glass Flask
40		Step 9	22 hrs	2/4/11 1:04 PM	2/9/11 10:04 AM	39	TK 5
41		Step 10	4 hrs	2/9/11 10:04 AM	2/9/11 3:04 PM	40	CL 1
42		Step 11	5 hrs	2/9/11 3:04 PM	2/10/11 11:04 AM	41	TK 1
43		Step 12	47 hrs	2/10/11 11:04 AM	2/18/11 10:04 AM	42	CL 4
44		Step 13	2 hrs	2/18/11 10:04 AM	2/18/11 1:04 PM	43	DR 1

Figure 5-1 Sample Gantt Chart Display of System Optimization Schedule[5]

Next, the data can be used for capacity planning and long-range schedule when combined with supply chain calculations for product changeover and optimal strategies.

---

[5] Example for illustrative purposes, not actual data

5.8. Sensitivity Analysis

Sensitivity analysis on the data indicates that the system is highly dependent on bottlenecks given shared equipment and a few long processing steps. The constraint of product contamination and processing area constraints significantly limit the potential utilization of the production facility. With the number of different products processed, only one product type can be running in the production area at a given time. However, multiple batches of the single product can be producing in the area.

5.9. Assumptions and Next Steps

Assumptions were made that the processing steps and average duration of Men A production is similar to the production of Men C, W-135, and Y, and Hib. However, each product has slight differences. For next steps of this project, this data can be compared to the actual processing times for the other intermediates and then optimized for future planning.

Cycle time variation and impact is often not well evaluated in manufacturing facilities. If desired, variability can be included in the model for steps shown to be significant in the sensitivity analysis. Failures in manufacturing, including this facility, are not historically random occurrences and adding a random generator of variability in the model is not recommended. Additionally, new products can be added to the model to review long-range schedule impact.

6. Supply Chain Calculations

6.1. Supply Chain in the Vaccine Industry

Supply chain management is very important to the vaccine industry because of the criticality and impact of unmet patient need. During an epidemic, the ability of the supply chain to react quickly and provide product directly relates to saving patient lives. A gap in available supply can result in loss of market share and diminished confidence by health care professionals and customers. For commodity products that can be sold by bid-and-tender, an insufficient supply can mean a loss of a large sale.

As described by Cohen, "*Too much inventory* is not a meaningful term to use when people's lives are at stake. [...] People's lives and health depend on an uninterrupted supply of medicine. Disrupting patients' lives by missing a sale is simply unacceptable." (55) Additional risks of improper supply chain management are detailed in Table 6-1.

Table 6-1 Risks of Improper Supply Chain Management in Pharmaceutical Manufacturing

• Shorting the market, patients do not receive product can be life or death situation
• Inability to react to a pandemic situation
• Losing market share
• Losing customers particularly through bid and tender business
• Increased product lead time
• Loss of confidence by customers, including end patient, health care professionals, payers, and global (WHO) and government organizations particularly for vaccines
• Increase of competitors from competitor companies receiving priority review status within regulatory agencies to bring competitive products to market earlier because the sole provider cannot meet market demand
• Added expense from cost of inventory

Typically, the industry has dealt with the importance of high service level requirements by simply having large safety stocks that are not strategically calculated based on cost and inventory using supply chain principles. Analytical supply chain calculations are even more

important as cost and availability to medicine are more constraining in the pharmaceutical industry, as shown in Table 6-2.

Table 6-2 Critical Business Reasons for Proper Supply Chain Management in the Pharmaceutical Industry

• High cost and value of inventory
• High impact of inventory loss
• Higher storage costs (e.g. from cold storage, product integrity, insurance)
• Product expiry and stability
• Risk of product loss (e.g. loss of product from a temperature excursion)
• Layers of protection analysis of inventory
• Cost of inventory

As shown in Figure 6-1, the expense of logistics for the high-priced goods of pharmaceuticals is low, but high compared to the weight of material being shipped. This value represents the added complexity of shipping products which need temperature controlled shipping, integrity control, tamper prevention/evidence, and have an increased risk of theft or integration of counterfeit products due to the product value. However, with higher development and manufacturing costs typical of the pharmaceutical industry, logistics costs as a percentage of sales average lower than other industries.

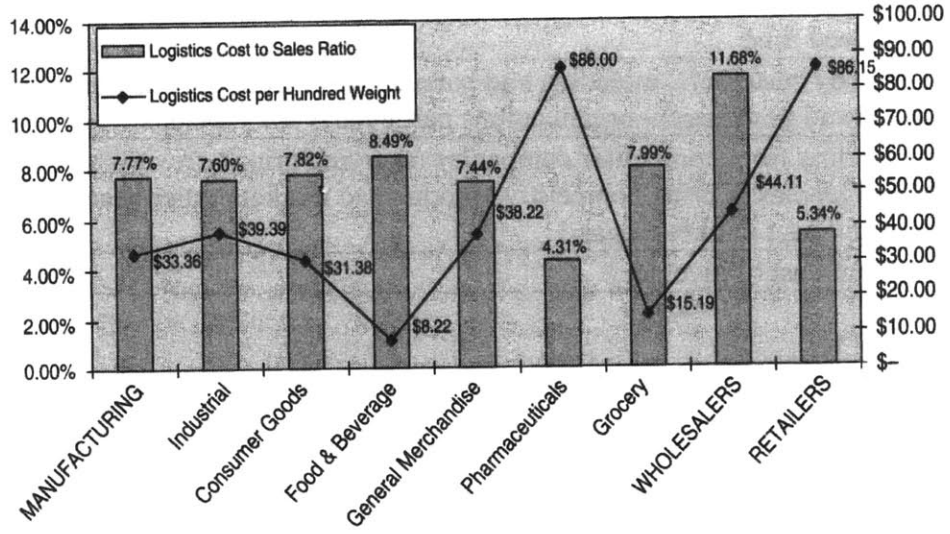


Figure 6-1 Logistics Expenditures Versus Sales for Various Industries (56)

6.2. Supply Chain Strategy

The "Newsvendor Problem" is a supply chain inventory management principle, described as when a newspaper deliverer has to choose in the morning how many newspapers to buy for the day. The decision is made by weighing the expected profit from the number of newspapers expected to sell during a given day against the loss from unsold newspapers. (Refer to Anupindi, et al. for a more detailed description of the newsvendor problem (57).)

For the pharmaceutical industry, capacity and supply chain capability decisions are made years in advance. Initial sales projections are made without any sales data; before the product is even approved for sale. Manufacturing facilities cost millions to build and qualify, and must be started years in advance (44).

However, the margins of most pharmaceutical products, compared to the cost of manufacturing, are so much higher than potential losses it is best from a business perspective to never run out of inventory. This trade-off is shown in Equation 4-1 for the evaluation of cost of overage/underage of manufacturing quantity (44) and Equation 6-1 for service level. Service level is a measure of the percentage of customers who will have product available upon request. For the pharmaceutical industry, this is typically very near 100%.

Equation 6-1 Service Level (57)

$$Service\ Level = Probability\ (Lead\ Time\ Demand\ \leq Reorder\ Point)$$

Margins are elevated for newer products because companies are given monopolistic status under patent laws for a period of time before generic competitors can enter the market with the same product. In a particular class of drugs, such as flu vaccines, an oligopoly is formed where a few companies offer similar, but not identical, products. Large markups over marginal cost are typical in the pharmaceutical industry, given the price elasticity of pharmaceutical demand (58) (55).

6.3. Promotion of Change

"*The central supply chain management group makes business decisions as well as manufacturing decisions.*" (55)

Previously, the inventory strategy was not analytically reviewed and supply chain was not detailing these business decisions. Just recently, the supply chain group started moving towards a strategic, but not analytical, level of finished inventory based on a certain number of months' demand. The intermediate inventory is also based on generalities and assumptions from past precedence rather than calculated values.

6.4. General Product Flow Through Manufacturing Supply Chain

A typical process flow through the manufacturing value chain for a cellular vaccine or biotech product is shown in Figure 6-2. First, cell strains are drawn from a bank, or collection of cells. Next, the cells are used to manufacture the antigen, or active ingredient produced, followed by purification of the product. The product may be then combined with diluents or lyophilized for product preservation, and sealed in a vial or syringe. Following this secondary production, the product is packaged into specific packaging for each market and distributed to customers through distribution centers, hospitals, pharmacies, and doctors (and additional methods in international settings)

The antigen manufacturing area is the focus of this project, but the project is integrated with incorporation of the full value chain.

Figure 6-2 Typical Manufacturing Flow for Biotech/Vaccine Production

An example flow for a given facility which produces a set of products is shown in Figure 6-3. Raw materials are manufactured into several products. Secondary production differs by product type and final product presentation, some product is sent to facilities for filling and lyophilization, others to liquid fill/finish into vials, syringes, and oral dose dispensers. Following secondary manufacturing, the product is packaged into different presentations for different customers, markets, languages, and regulatory requirements and distributed. Throughout the process, third party manufacturers may be qualified as an option to in-house production or bulk product can be sold to another retailer for completion of the remainder of the processing.

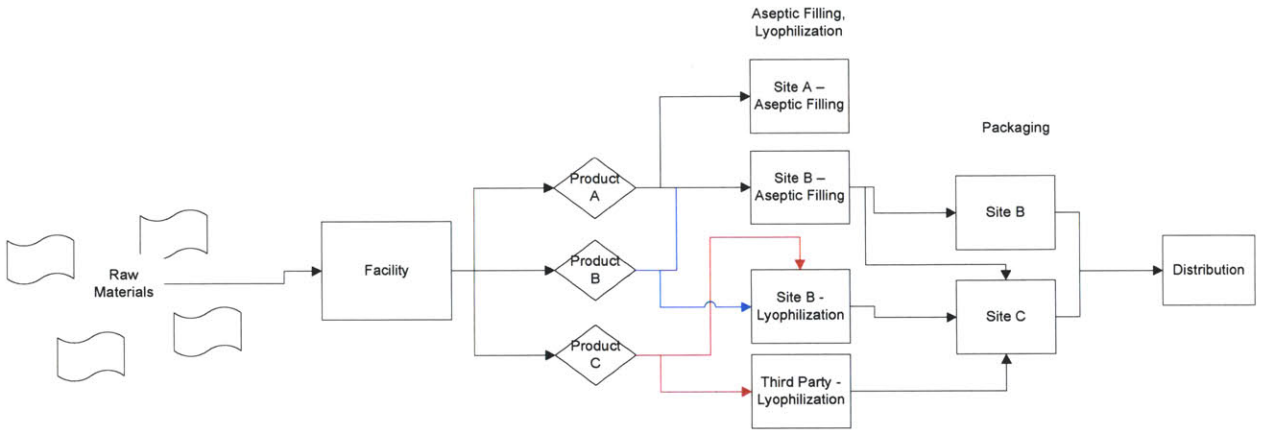


Figure 6-3 Vaccine Sample Supply Chain Diagram[6]

The complexity of the product manufacturing increases substantially down the value chain. In secondary production, the product can be produced in multiple different presentations, for example, a product can be developed for use in a single-dose vial, a multi-dose vial, a prefilled-syringe, or combined with other antigens for a multi-valent vaccine. Vaccines are packaged with a slight *overfill* to ensure the health care provider has sufficient product to dispense to the patient. The overfill amount is dependent on product presentation and number of

[6] Example for illustrative purposes, not actual data

doses in container; these permutations in secondary production add variability and uncertainty to the capacity and number of doses per gram of antigen produced in primary manufacturing.

6.5. Novartis Vaccine Supply Chain

The antigen manufacturing facility analyzed for this project produces four different antigens for Meningitis; Men A, C, W-135, and Y; as well as Hib. The facility also produces an intermediate called CRM to conjugate the antigen.

Menveo is presented to the patient with a liquid vial containing Men C, W-135, and Y with a freeze-dried vial of Men A. Menjugate is a lyophilized vial of Men C. To produce these, Men C, W-135, and Y for Menveo are sent to aseptic fill and finish to be filled into a single container containing all three antigens (43). Men A for Menveo, as well as Men C for Menjugate, are sent to a lyophilization facility (43). In packaging, the lyophilized Men A is reunited with the vial containing Men C, W-135, and Y and packaged together. Other necessary components are added during packaging depending on the product and the market of sale, including diluent, needles, and product information inserts.

As shown in Figure 6-4, Figure 6-5, and Figure 6-6, each product is available in multiple forms of dosing and product presentations.

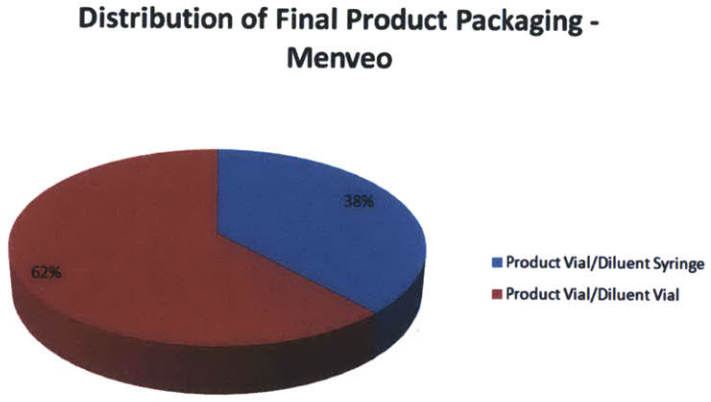


Figure 6-4 Distribution of Final Product Packaging – Menveo[7]

[7] Example for illustrative purposes, not actual data

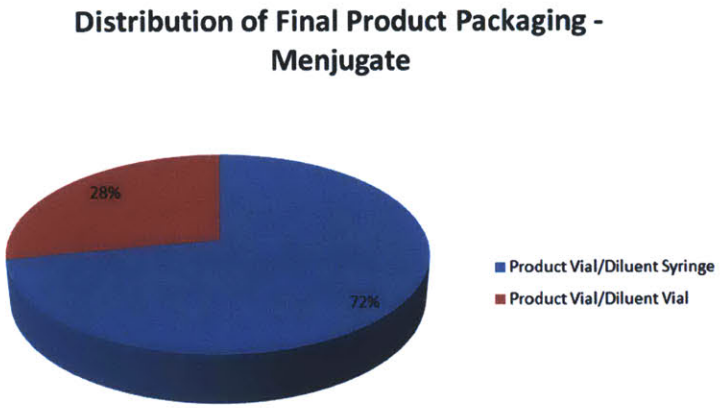


Figure 6-5 Distribution of Final Product Packaging – Menjugate[8]

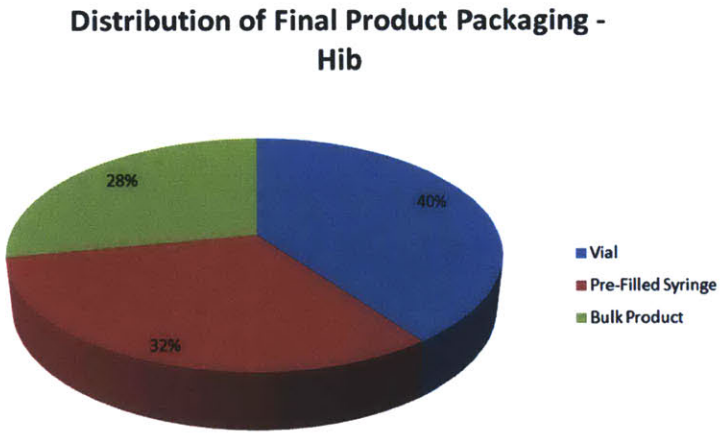


Figure 6-6 Distribution of Final Product Packaging – Hib[9]

[8] Example for illustrative purposes, not actual data
[9] Example for illustrative purposes, not actual data

6.6. Demand

The demand profile is twofold from the perspective of the antigen manufacturer: actual consumer demand, and downstream secondary production demand.

6.6.1. Market Demand Predictions

Projected consumer demand for products are typically produced by a sales or other external group and translated to manufacturing and supply chain for production and capacity planning. Significant uncertainty exists in anticipating demand of products in progress for entry into new regions, new indications for product use, epidemic threats, and expansion with growing disease levels. In Figure 6-7, an illustrative example shows the projected effects of product growth and contraction over time on a per-antigen basis.

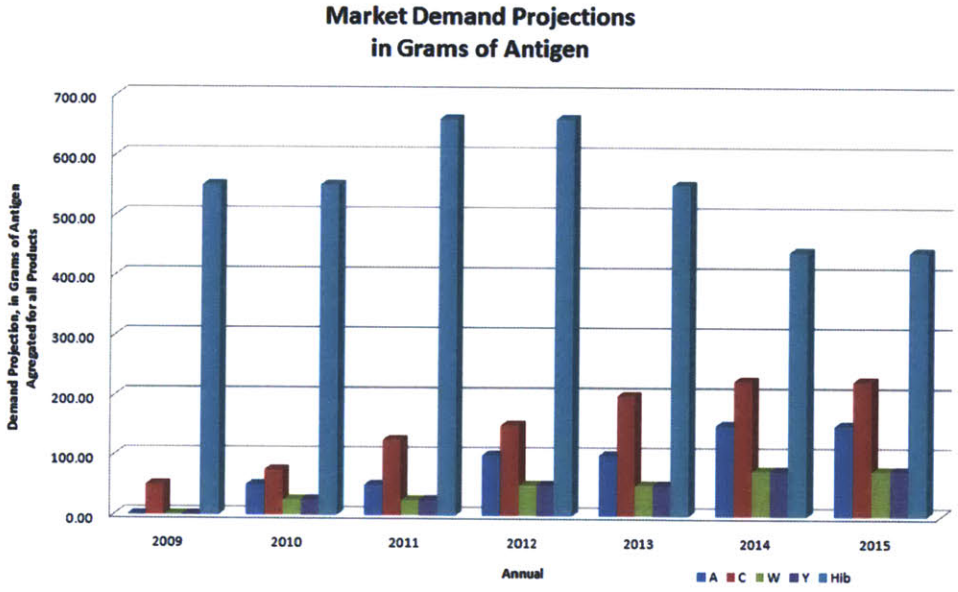


Figure 6-7 Market Demand Predictions, in Grams of Antigen[10]

[10] Example for Illustrative Purposes, Not Actual Data

6.6.2. Secondary Manufacturing Production Demand

As only limited options are available for secondary production, this "demand cycle" can be communicated to the manufacturer and is based on production scheduling for downstream customers. Demand may also not be level over the year because the plant processes other products, such as flu vaccines which may have capacity-restricting seasonal demand, or from a seasonal shutdown. As described above, the processing options and containers for secondary production impact the number of doses a given amount of bulk antigen fulfills. Figure 6-8 and Figure 6-9 illustrate the irregular demand in downstream processing for a vial and syringe filling facility and for a lyophilizing facility.

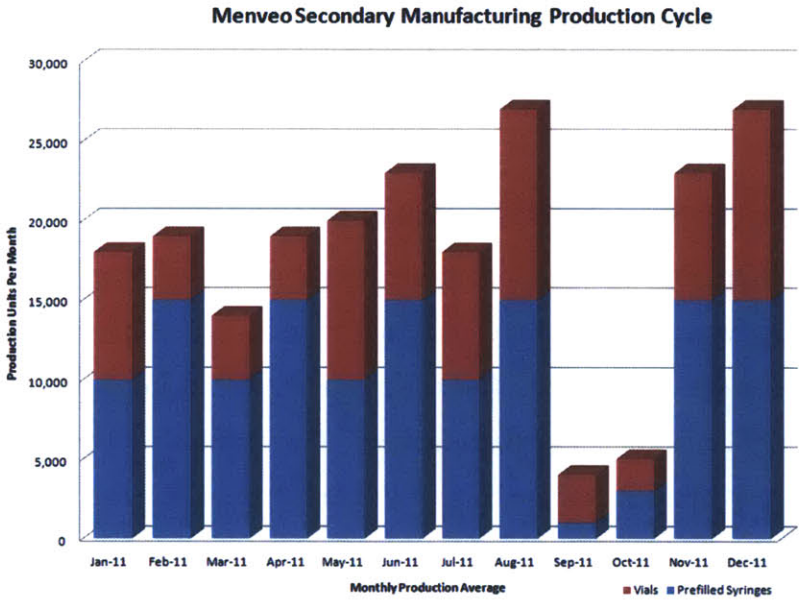


Figure 6-8 Menveo Downstream Manufacturing Production Cycle[11]

[11] Example for illustrative purposes, not actual data

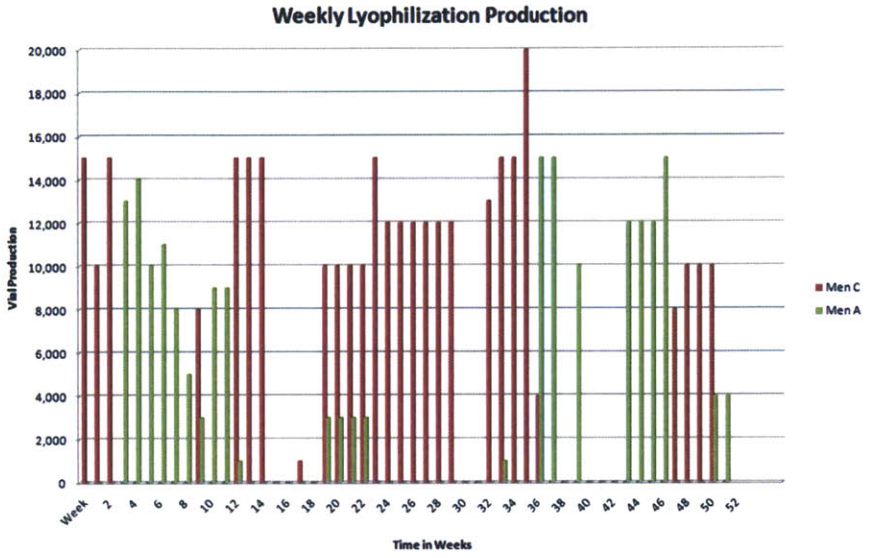


Figure 6-9 Annual Lyophilization Production, Aggregated Weekly[12]

6.7. Final Inventory Characteristics for Multi-Valent Product

For the Rosia bulk facility, multiple antigens are manufactured on shared process equipment. For Menveo, all antigens are needed to produce final product. Each antigen must be manufactured individually because the equipment is shared; upstream capacity limitations and capital cost tradeoffs dictate that product cannot be manufactured simultaneously. Therefore, intermediate inventory must be held until all components are available. To determine service level of final bulk product, each required component must be available and there are no partial benefits to providing incomplete inventory quantities needed for a unit of product.

[12] Example for illustrative purposes, not actual data

6.8. Calculations

The dynamics described above are collated and analyzed in the following supply chain calculations. The aggregate of these calculations are shown in Figure 10-1 Supply Chain Analysis Dashboard as an easy to use review of parameters by management, planning, and supply chain groups.

6.8.1. Reorder Point

The theoretical inventory level at which production should begin for a given product is when the inventory level is equal to the amount of inventory needed to maintain safety stock (SS) plus the amount of inventory needed to cover demand during production cycle, or lead time demand (LTD). The analysis is completed for only the production lead time of producing the given material, excluding raw material delay and assuming production can begin immediately of needed components.

Equation 6-2 Reorder Point

$$ROP = LTD + SS$$

6.8.2. Safety Stock Based on Demand

Safety stock is a critical parameter for establishing the availability of product. The safety stock level, SS_{level}, should be determined by analyzing risks of product shortage, uncertainty of demand, and capability risk in production.

The desired safety stock level in this area is established based upon a certain number of months' expected demand. This project is focused on the safety stock as calculated for bulk antigen only, not final packaged product. Based on the length of production and demand calculation dynamics, demand rate for safety stock calculations is based on the average of year and year + 1 demand projections.

Equation 6-3 Safety Stock as a Fraction of Demand

$$SS = \left(\frac{D_n + D_{n+1}}{2}\right)\frac{SS_{level}}{12\ months}$$

6.8.3. Production Lead Time

Understanding production lead time is important to understand how rapidly the company can react in a pandemic situation. Production lead time for bulk product, calculated here, is not affected by downstream processing options. The amount of product needed to cover the economic production quantity during a production cycle is equal to the demand rate times the duration of production to make the economic production quantity (EPQ).

Equation 6-4 Production Lead Time for Economic Production Quantity

$$LT_{EPQ} = EPQ \times \frac{cycle\ time}{batch} \times \frac{D}{t}$$

$$EPQ = Economic\ Production\ Quantity\ in\ Batches$$

$$D = Demand\ in\ Batches$$

$$\frac{D}{t} = Demand\ Rate\ in\ Batches/Time$$

Since a partial batch cannot be produced[13], the economic production quantity is rounded up to the nearest whole batch.

Equation 6-5 Production Lead Time

$$LT_{EPQ} = EPQ(roundup) * t_{batch}$$

---

[13] In the pharmaceutical industry, regulatory documentation is typically produced specifying batch size(s) that are available for production options, as changes in the size of batch size within a set of facility equipment dictate the capability of producing product.

6.8.4. Economic Production Quantity (EPQ)

The economic production quantity is the number of sequential batches that should optimally be made of a given product in a campaign before switching to the next product. It does not impact the size of an individual batch. In the pharmaceutical industry, the contamination constraints between different products, cleaning between batches, constrained order of operations, expense of resin, filters, and product-specific equipment creates a different trade off scenario for product changeover when compared to other industries.

Similar to the economic order quantity (EOQ), this calculation balances the cost of changeover between two products and the cost of inventory holding. The trade-off between the setup cost per production run and the carrying cost of the produced inventory is shown in an example by Frazelle (56) in Figure 6-10.

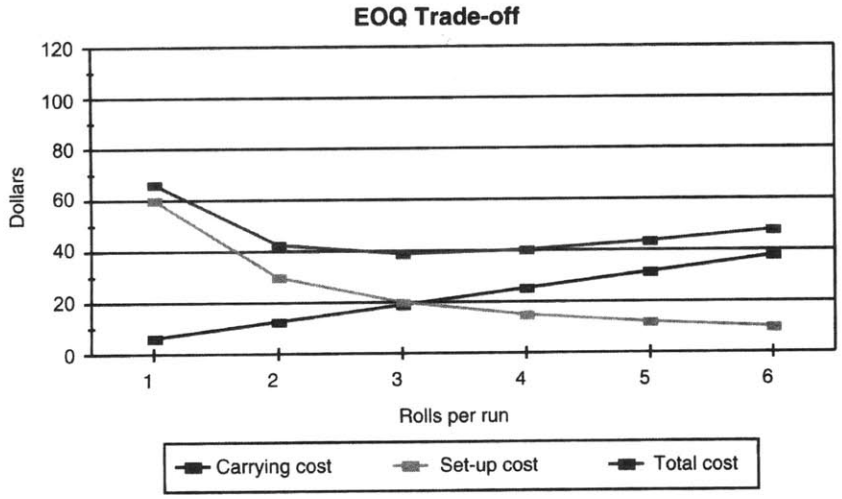


Figure 6-10 Economic Order/Production Quantity Trade-off (56)

The economic production quantity is equal to the square root of the product of twice the changeover cost times the annual demand divided by the holding cost of inventory.

Equation 6-6 Economic Production Quantity

$$EPQ = \sqrt{2\,A\frac{D}{h}}$$

$$A = changeover\ costs\ from\ one\ product\ to\ another$$

$$D = Annual\ demand\ in\ batches$$

$$h = per\ unit\ holding\ costs\ in\ {}^{\$}/_{unit\,\cdot\,time}$$

Equation 6-7 Holding Cost

$$h = h' \times MV_g \times y$$

$$h' = holding\ cost\ as\ a\ \%\ of\ product\ value$$

$$MV_g = Market\ value\ of\ product\ in\ \$\ /\ g$$

$$y = average\ yield\ in\ {}^{g}/_{batch}$$

The holding cost of inventory is typically estimated at 20-50% of the cost of the item (59) (60) for capital costs, taxes, insurance, storage, and disposition. A sensitivity analysis of the holding cost and changeover costs (or fixed order cost, in EOQ model) is described in *Building Intuition* (60). Holding cost is calculated in this equation with the assumption of a proportional relationship to the value of the inventory. For a review of evaluation by size of inventory, refer to Silver, et.al.(41).

6.8.5. Doses per Batch

The number of doses that can be produced from a single batch of an antigen is calculated based on average yield and number of grams needed per mds.

Equation 6-8 Doses per Batch

$$Doses\ per\ batch\ (\frac{mds}{batch}) = \frac{mds\ of\ Product}{batch\ of\ antigen}$$

$$= \frac{average\ yield\ per\ batch\ of\ antigen\ (\frac{g}{batch})}{grams\ of\ antigen\ needed\ per\ mds\ of\ Product\ (\frac{g}{mds})}$$

6.8.6. Value of Product per Gram

The value per gram of product produced can be calculated based on the value of product and grams used per dosing unit. Assumptions are made that fixed costs are established and distributed proportionally to yield; additionally the products produced in this facility are adequately assumed to have operationally similar levels of complexity, and that most variance from product value is from yield. For multi-valent products, such as Menveo, an aggregate calculation was developed to combine the cost of production for each antigen into a collective weight.

This parameter is valuable for comparing the cost of production for various types of products, making decisions on which products to increase investment in, outsource, or for prioritizing against other products in a portfolio or given facility.

Shown below are equations for Market Value of Product per Gram. Similar equations can be used for reviewing internal valuation of cost of goods sold and added value or cost in a given processing area, per gram of product.

Equation 6-9 Market Value of Product per Gram

$$MV_g = \frac{Market\ value\ of\ product\ in\ \$}{g\ of\ antigen\ in\ product}$$

$$MV_g(Monovalent) = \frac{S}{D * {}^{g}/_{mds}}$$

$$= \frac{Projected\ sales\ (\$m)}{Demand\ (mds) \Big/ Grams\ of\ antigen\ per\ mds\ \left(\frac{g}{mds}\right)}$$

$$MV_g(Multivalent) = \sum_{\substack{antigens \in \\ Product}} \left(\frac{S}{D * {}^{g}/_{mds}} * C_{\%antigen} \right)$$

$$= \sum_{\substack{antigens \in \\ Product}} \left[\left(\frac{Projected\ sales\ (\$m)}{Demand\ (mds) \Big/ Grams\ of\ antigen\ per\ mds\ \left(\frac{g}{mds}\right)} \right) \% of\ costs\ by\ antigen\ (\%) \right]$$

6.8.6.1. Percentage Cost of Bulk Multi-Valent Product by Antigen

For multi-valent products, the production costs are not evenly distributed among antigens. Calculation of the cost of bulk multi-valent antigens requires proportionate collection of costs. The assumptions described above are held, that most variance from product value is from yield.

Equation 6-10 Percentage Cost of Bulk Multi-Valent Product by Antigen

$$\%\ of\ cost\ of\ Multivalent\ Product\ by\ antigen = \frac{\frac{mds\ of\ Product}{batch\ of\ antigen}}{\sum_{\substack{antigens \in \\ Product}} \left(\frac{mds\ of\ Product}{batch\ of\ antigen} \right)}$$

6.8.7. Optimal Number of Campaigns per Year

Production needed in batches (with annual inventory review cycle), divided by economic production quantity represents the optimal number of annual campaigns of a given product to meet demand. As discussed in Section 6.9, the product changeover strategy for a campaign facility is critical for lowering inventory costs while balancing product changeover expense and time.

Equation 6-11 Optimal Number of Campaigns per Year

$$Annual\ Campaigns = \frac{P(batches)}{EPQ}$$

6.8.8. Production Needed in Given Inventory Review Period

Production needed is calculated in units of grams or batches, to meet projected demand with accommodation for current inventory levels. The supply chain is set as a periodic review with an "order up to" strategy to meet safety stock level and demand expectation, accounting for current inventory level. This is described as a *Replenishment Cycle* or *Periodic-Review, Order-Up-To-Level* system (41).

In the supply chain scenario described in Sections 6.4 and 0, the production system for both primary and secondary production is campaigned production with variations for internal demand use by downstream processing. Over a given time period the inventory level will fluctuate between the upper bound of safety stock plus demand over periodic review cycle time, and lower bound of the safety stock level. The inventory level will be step functions for both increases and decreases, showing an aggregate change in stock level with campaign production.

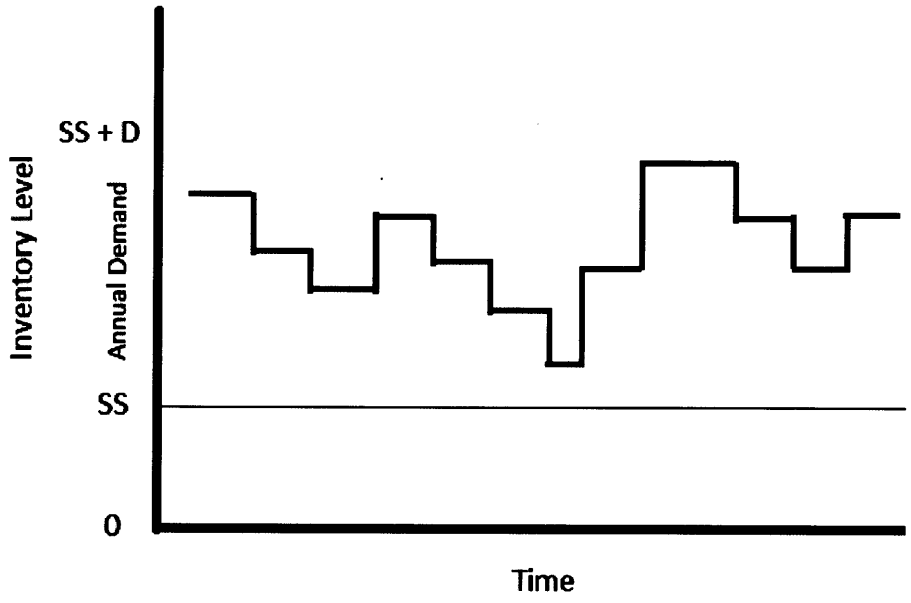


Figure 6-11 Inventory Level of Intermediate Product with Campaign Processing of Upstream and Downstream Manufacturing

The amount that should be processed until the next periodic review cycle is calculated in Equation 6-12. The period demand less the current inventory plus the required safety stock level is equal to the amount of production needed during the period until the next review.

Equation 6-12 Production Needed

$$P = D - I + SS$$

6.8.9. Demand in Units of Grams or Batches

Demand projections are typically provided in number of doses needed. The number of doses is converted to grams and batches required for production by using the number of grams per million doses and average process yield. Uncertainty is added in this calculation because the number of grams per million doses varies by dosing presentation; overfill of package to confirm sufficient material for dosing, and because process yield is an average. This can be represented

as a single parameter, as shown with the overfill parameter in Equation 6-13, or by creating a model to simulate variability.

Equation 6-13 Demand, in units of Grams Needed

$$D(g) = \sum_{\substack{products \in \\ antigen}} \left(demand\ in\ mds \times \left(\frac{g\ Recipe}{mds} + \frac{g\ Overfill}{mds} \right) \right)$$

Equation 6-14 Demand, in units of Batches Needed

$$D(batches) = \frac{D(g)}{Yield\ \left(\frac{g}{batch}\right)}$$

6.9. Product Changeover

Frequency of product changeover, as shown in economic production quantity and optimal number of campaign calculations, is an important parameter to balance inventory expense, cost of changeover, and overall facility utilization.

The pharmaceutical industry is economically restricted against making one unit of product A, then a unit of product B, as on a true pull system. In comparison to an automobile manufacturer producing "red van, blue car, white truck" sequentially on a manufacturing line, it would be "one dose of product X, one dose of product Y, one dose of product X" which is prohibitive from a capital expense as well as regulatory contamination concerns.

However, the production capability to be readily flexible and able to switch between products is a valued trait that should be adapted more heavily in the industry. The results include better operator training, strengthened capabilities, improved rigor for utilization of SOPs and BPRs.

Table 6-3 Dynamics of Product Changeover

• Product change over decreases available production time
• Contamination constraints limit ability to produce batches of different product sequentially
• Cleaning time increases processing step duration, cleaning time typically increased during product changeover to new product versus product ran in prior batch
• Product changeover in the pharmaceutical industry has different cost tradeoffs from other industries because of cost of inventory and cost of changeover

Table 6-4 Benefits of Increased Product Changeover

• Decreased inventory holding
• Operator capabilities for changeover and training increase with repeated activity
• Capabilities become broader as operators gain expertise on full process with variety of product expertise (e.g. eliminates situations where operator has not ran processing product in six months)
• Increase use and improvement of procedures, training, and following instructions in batch production records.

6.10. Risk Management

With uncertain demand, lead times, and complex manufacturing facilities, significant risks exist in pharmaceutical supply chain management. These risks can be mitigated with techniques as exhibited in Table 6-5.

Table 6-5 Risk Management Mechanisms in Pharmaceutical Manufacturing

• Complete stability testing for long product shelf-life
• Salvage excess product inventory through bid-and-tender business
• Produce excess inventory early to hedge exceeding demand, and change future production according to actual demand
• Develop multi-product facilities to plan capacity to meet for average demand for multiple products
• In-source new molecules to fill capacity from underutilized manufacturing facilities
• Serve as third-party contract resource for other companies[14]

[14] To begin production a third-party contract resource would be a significant change in strategy for a facility and significant consideration would need to be evaluated before pursuing this option.

6.11. Intermediate Work-in-Progress Inventory

Often, intermediate inventory is held within a given facility. This strategy should also be approached analytically. Table 6-6 and subsequent sections discuss the advantages and strategies to holding, or not holding, intermediate inventory.

Table 6-6 Reasons to Hold Intermediate Inventory

1. Keep inventory at more stable hold point
2. Hold inventory at less expensive holding point
3. Postponement of downstream manufacturing choices(56)
4. High value is added to the product at a downstream step
5. Smooth production scheduling

6.11.1. Stability Hold Point for Prevention of Product Degradation

In industries with product degradation such as the pharmaceutical industry, hold times and product stability are important considerations in determining inventory holding location. Holding inventory earlier can allow for use of multiple holding durations and delay processing decision and expense for manufacturing product to fill high-variability demand scenarios.

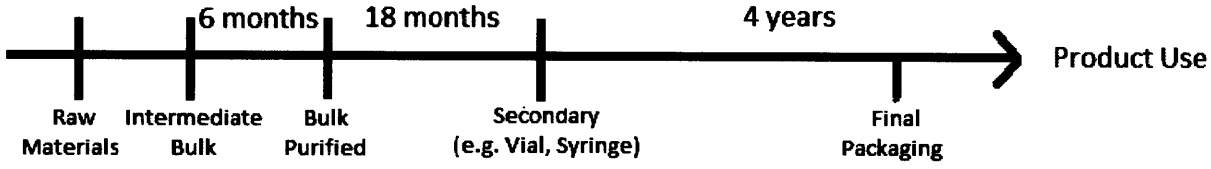


Figure 6-12 Sample Stability Hold Points for Pharmaceutical Products [15]

[15] Example for illustrative purposes, not actual data

6.11.2.Decrease Holding Cost

For a manufacturing process where the product is decreasing in size through progression of the manufacturing steps, as is common in purification of bulk pharmaceuticals, holding costs can be reduced by processing to a smaller volume to then reduce costs of inventory temperature control, storage space, and transportation.

Holding costs can vary dramatically by the requirements of holding step. Storage expenses, in refrigeration equipment cost as well as energy cost, increase as the temperature decreases from ambient as shown in Figure 6-13 and Figure 6-14.

Refrigeration Temperature, °C	Number of Stages Required	Cost of Refrigeration, $/t
6.6–4.4	1	800
(−28)–1.1	1	1500
(−45)–17.7	2	1800
(−84)–(−45)	Multistage	4000–5000

Figure 6-13 Estimated Refrigeration Equipment Cost as a Function of Refrigeration Temperature (61)

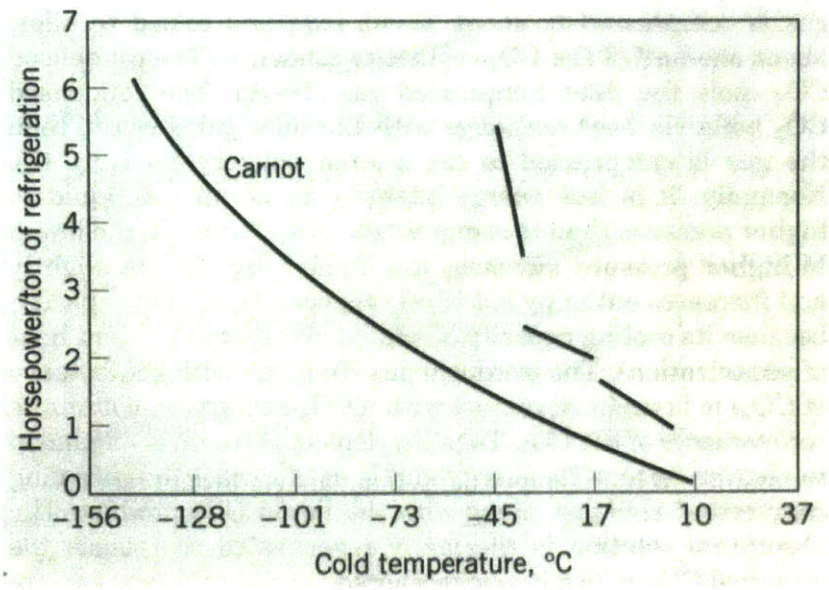


Figure 6-14 Energy Utilization as a Representative of Cost (61)

6.11.3.Postponement

For manufacturing processes where the intermediate component is used in multiple products, holding inventory before the decision step, rather than after, allows for smaller amounts of inventory to be held at the same customer service levels. An example described by Chopra and Meindl shows how Dell postpones assembly of final product variability with a pull system, only after a customer has ordered. This process results in smaller amounts of safety inventory of finished goods and lower inventories of each component than a manufacturer that assembles to stock.(45)

For Novartis, the products manufactured in the bulk facility are specified at the time manufacturing begins, and postponement is not a value-added reason for intermediate inventory holding. However, holding inventory before secondary production and packaging is a valuable form of postponement before determining the final delivery formation, packaging, and destination.

6.11.4.Delay Value Added Step

If a particular step is resource intensive or uses expensive raw materials, holding inventory before, rather than after the step, reduces overall risk and cost of inventory holding. Because the value of the inventory is lower, insurance cost and product loss risk decreases.

6.11.5.Production Smoothing

Holding inventory before a production bottleneck can reduce impact of an outage of the production step (41) and decreased overall capacity throughput. For a production step with an expected failure rate, holding work-in-process (WIP) inventory after the step can reduce disruptions for downstream processing. WIP inventory helps maintain a constant workflow, which balance personnel needs and keeps equipment utilization.

The fourth principle described in *The Toyota Way* is "Level Out the Workload" (5). Elimination of *Muda, Mura,* and *Muri*, or waste, unevenness and overburden are applicable principles across manufacturing. While it is not economically feasible for the pharmaceutical industry to produce at the pull level of demand as the auto industry, high level of resistance to creating shorter campaigns and batches exists in the industry.

7. Organizational Dynamics and Change Implementation

7.1. Introduction

As described by Klein in *True Change*, understanding the culture of the current organization is a means to facilitating change (62).

7.2. Measurement of Change within Organization

A component of change implementation in an organization is determining metrics to measure during the process. Table 7-1 shows metrics to track before and after change implementation, some of which are commonly tracked during production and others which are more detailed during change observation.

Table 7-1 Metrics for Analysis During Change Implementation

• Factory losses
• Deviation or excursion rate per lot
• Production rate
• Product yield
• Variability, tracked with process control charts(63)
• Error rate
• Personnel turnover
• Morale
• Training skills across departments, Job role changes internally
• Modifications to process documentation (e.g. SOPs, BPRs, training)

7.3. Worse-Before-Better Effect of Change Implementation

Oftentimes, a system will display a worse-before-better response to a change. This is frustrating and counterintuitive to organizations and inhibits long-term growth. As shown in an example from Keating, et.al. in Figure 7-1, the cost savings of a preventative maintenance program are negative (the program costs more than it saves) for a period of time before the root cause of integral problems are fixed and savings are realized.

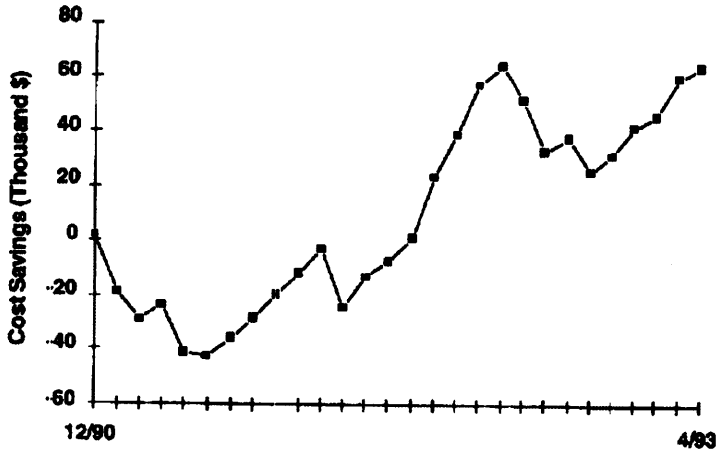
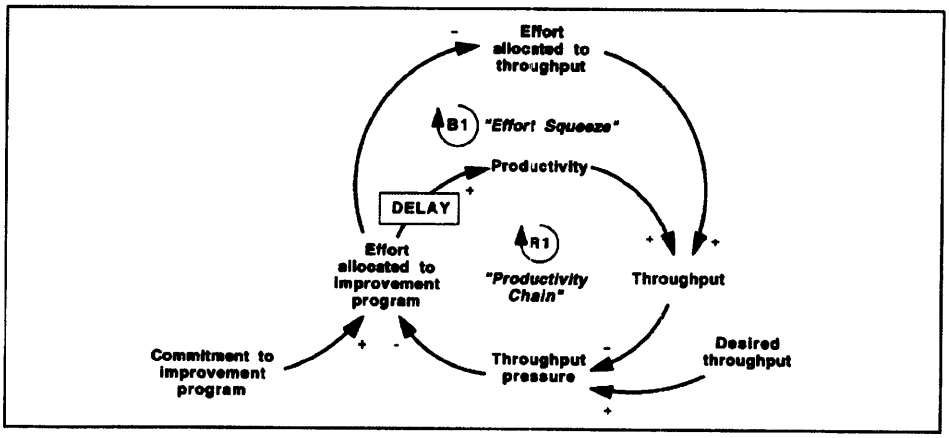


Figure 7-1 Worse Before Better: Cost Savings of Improvement Program (64)

The systems that create this effect can be displayed effectively in a system dynamics diagram. Two loops create this effect, where the balancing "Effort Squeeze" loop causes an increase in costs before the delayed reinforcing "Productivity Chain" loop counteracts the balancing loop.



Improvement can be Self-reinforcing.
Arrows indicate the Direction of Causality: Signs (' + ' and ' - ') at Arrowheads indicate the Polarity of Relationships: A ' + ' Denotes that an Increase in the Independent Variable Causes the Dependent Variable to Increase, Ceteris Paribus (and a Decrease Causes a Decrease). Similarly, a ' - ' Indicates that an Increase in the Independent Variable Causes the Dependent Variable to Decrease. Time Delays are Indicated in the Diagram by a Delay Box. Reinforcing Loop Polarity (Denoted by R in the Loop Identifier) Indicates a Self-reinforcing (Positive) Feedback Process. Balancing (B) Loop Polarity Indicates a Regulating (Negative) Feedback Process

Figure 7-2 Improvement Project Cycle System Dynamics Diagram (64)

In the examples of change recommended in this paper, a potential worse-before-better scenario could occur with implementation of more frequent product changeovers. The increase of change into the manufacturing system may temporarily cause increased workload and abnormal process occurrences, but this is before the impact of improved documentation, increased capabilities and cross training, and before agile work systems provide for increased abilities.

7.4. Implementation of Change within Organization

The concepts of implementation of change as an outsider-insider of an organization is extensively detailed in Klein, *True Change* (62). As explained by Klein, getting to know the existing culture is a "key lever in helping others to see where underlying assumptions are getting in the way of overcoming challenges," (62). It is important to understand the organizational structure, the levers within the organization for understanding change, and how to introduce concepts at the right time. To do this, the Italian culture and the Novartis organization were

Many generalized observations were considered for change analysis when reviewing the Italian and Novartis cultures.

7.4.1. Italian Culture

Italian culture is dominated with relationships of people, and many artifacts from the Italian culture are maintained at the Rosia and Siena sites. Klein's discussion of relationships and networks are important facets to change implementation in a heavily relationship-oriented culture (62).

First, the lunches in the cafeteria are highly subsidized and provide four courses to maintain the large meal eaten during a typical mid-day siesta. The Italians eat the entire *primi* pasta course first before progressing to the typically meat-based *secondi* and then the side dishes or *contorni*, vegetables or *verdure*, and *dolci*, or dessert. People eat with the same group of friends (not necessarily co-workers) each day at the same time, and never eat at their desk or alone. Conversations are very strongly focused on relationships and people, and rather than

work. The cafeteria is only a place for the mid-day meal, not for other meetings or discussions during the day as may be observed in an American cafeteria. At other times of the day, espresso and cappuccino breaks are important times to refresh and chat with others. At work, there is no voicemail, but people have cordless desk phones – not cell phones – to be reached in the facility.

The importance of relationships is built into the culture outside the cafeteria also. Outside of work, stores, museums, and even an occasional hotel swimming pool, have siestas and close in the afternoon for rest and time for lunch. Dinners are long and include much conversation between the many delicious courses. Servers do not interrupt until the course is finished, and the check must be requested upon completion of the meal. Italian restaurants are set up to have one party per table, per night, compared to American restaurants that plan for 3-4 changeovers a night per table. The focus on people and relationships over money is refreshing.

At the plant site, the management business is conducted in English, but the operations are predominantly Italian language, including documentation. Key leadership personnel brought in from other countries are given lessons in Italian to help build skills and efficiency, as well as integration into the community.

7.4.2. Novartis Organization

The Vaccines division of Novartis is in a start-up/turnaround mode as an artifact of company culture. Culture is an area that is particularly cultivated; special representatives are trained in culture development across the sites. The development of a unified and unique Novartis culture is difficult. People are joined together from different countries and cultures; some people worked previously for other pharmaceutical companies or other divisions of Novartis, others were long-term Chiron employees and worked for a decade or more in a single facility or job position. Some employees have long working relationships together across multiple corporations and have now rejoined at Novartis.

This dynamic of experienced people, particularly in Holly Springs and in the global groups, has created a strong wealth of information, leadership and technical abilities for the company. With this knowledge, the employees and management are able to draw from the best practices of many companies and work together collaboratively. Significant travel and flexibility

are valued in many roles of this start-up culture. Novartis has created an open space policy where employees have open desks, eliminating enclosed cubicle walls with typically one-wall per desk and some areas have open cubes where people just come for a day or out while travelling.

In addition to attracting quality employees, the American-headquartered division called Novartis Vaccines and Diagnostics was built with help from many investments from the parent company, Novartis AG of Switzerland, accelerated growth and revenue from a flu pandemic, and funding from the US Federal Government. Senn-Delaney is a culture-development focused consulting firm that Novartis uses to build and shape a culture for the new corporation. IQP – an acronym for innovation, quality, and productivity – is used to implement projects with lean and six sigma tools across the organization, with a structure to develop and progress ideas throughout the organization.

The relationship with the parent company at the individual employee level is still forming. Some information technology systems are not fully linked between NVD and the Novartis Pharmaceuticals division. One social networking tool, Yammer, joins people across sites across the 100,000 person organization that would normally not be connected and makes it nearly effortless to rapidly share knowledge. Similarly, the linkages between NVD and Novartis Pharmaceuticals are limited within manufacturing and supply chains. The business could potentially capitalize on economies of scale in purchasing of items and distribution. However, the organization has chosen to forego these cost benefits to gain the ability of distinguishing business segments and financial structures.

7.5. Impact of Project Dynamics in Change Implementation

Implementation of this project has the most significant potential to impact the operations group. Operators will likely have more work with these solutions, but potential for more leveled work production and increased capabilities, which mean less hiring and firing of temporary workers and building of skill sets for future roles. More cross-training allows for more flexible production scheduling and possibly lowering the number of operators on staff at a given time.

For example, if area A needs 2.5 people, and area B needs 1.5, and people were cross trained, it may be possible to have 4 people total rather than 5 on staff at a given time.

This project also changes some of the norms for the organization by breaking conventions of current operational times and production breaks by looking at the process from the equipment instead of within current structural bounds. This involves political ties but can be improved by leveraging relationships with Operations Managers and long-term people with value and respect in the organization. Also, a few of the proposals made are forward-looking, and the facility is not ready for all changes at the same time while many other projects are being implemented.

8. Recommendations and Conclusions

8.1. Capacity Modeling

Many great software tools exist for capacity modeling within the pharmaceutical industry. As multi-product facilities become more common, understanding capacity constraints and modeling scenario distribution with incorporation of all products the value of keeping current models for product evaluation grows in value.

8.2. Cycle Time Optimization

Using system optimization techniques is currently infrequent in the pharmaceutical industry. Understanding the binding effects and sensitivity analysis of modifying constraints with sensitivity analysis opens new arenas for operational efficiency and lowered cost of production. Scheduling in a multi-product facility is increasingly complicated and matrixed; analytical tools such as optimization provide strategic, clarifying focus on improvement areas.

8.3. Supply Chain Analysis

Implement periodic review of supply chain across product value chain and at the site level. Begin by evaluating existing performance against calculated parameters and implementing change progressively at areas of most value, particularly changes that also integrate operational improvements. Include supply chain calculations and strategically make decisions uniting across business units – supply chain, manufacturing sites, manufacturing strategy, third-party manufacturing outsourcing management, and sales/demand predictions. Review inventory holding strategy, economic production quantity and length of campaign, cost of product manufacturing over time as facility utilization and capacity increases.

8.4. Organizational Dynamics and Change Implementation for Novartis

Continue focused development of new and integrated culture as the organization grows and ends the turn-around phase after acquisition of Chiron and new facility start-up in Holly Springs, NC. Attention to political dynamics, including international cultural differences, working relationship between key leadership personnel, previous experiences at other

pharmaceutical manufacturers, and relationship with former Chiron employees should continue to strategically evolve. A shift of the organization will occur after organization stabilizes out of start-up/turn-around dynamic, and the leadership techniques and personnel needed to sustain the organization will have different skills and motivations. These changes are in concurrence with advances in the industry and rapid changes in vaccines.

8.5. Conclusion

In summary, application of techniques such as capacity modeling, cycle time optimization, and supply chain analysis can provide impactful value to pharmaceutical, vaccine, and biotechnological manufacturing. With increased cost pressures, growing number of multi-product facilities, and product specialization, the industry complexity is growing and the use of analytical tools is necessary to drive excess waste out of organizations. The calculations and trade-off points may differ for the pharmaceutical industry than from other industries, given market exclusivity, higher margins, contamination and product integrity concerns, but the potential impact is growing with added complexity and integration of the manufacturing chain.

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10.Appendix

10.1. Appendix A: Modeling Software Comparison Analysis

Table 10-1 Modeling Software Comparison

Name	Description
Arena	Manufacturing Simulation Software. Complex, medium to large-scale projects involving highly sensitive changes related to supply chain, manufacturing, processes, logistics, distribution, warehousing, and service systems.
ASPEN Plus	Process modeling tool for conceptual design, optimization, and performance monitoring particularly for chemical-based industries
ChemCAD	A process flowsheet simulator. Full suite of tools for simulating steady-state or dynamic chemical processes. Handles batch, semi-batch, and continuous systems.
CF Design	Simulates fluid flow and heat transfer
CFX - Ansys	Computational Fluid Dynamics
CPLEX	Large-scale mathematical programming software and services for resource optimization.
Excel - Crystal Ball add-in	Spreadsheet-based application suite for predictive modeling, forecasting, simulation, and optimization.
Excel - @Risk add-in	Performs risk analysis using Monte Carlo simulation
Flying Logic	Visual-based planning software
GAMS	High-level modeling system for mathematical programming problems.
Gurobi	High-level linear programming
Gusek/GLPK	An open-source solver which uses GLPK linear programming solver
Hysys	Acquired by Aspen and Honeywell and is now integrated into UniSim
Opal	Control system engineering, modeling and simulation software products
Uniformance PHD	Integrates with data servers (OPC, Honeywell, third party)
Process Model	Modeling software
ProModel	Graphical manufacturing system simulation software. Full graphical simulation of production systems with animation are possible
ProModel - Orchestrate Plug-in	Orchestrate Scheduler – Enables ProModel to be used as the simulation engine under a finite capacity scheduling application.
ProModel - Process Simulator (Visio add-in)	Good for lean/six sigma and process mapping

MODSIM	Simulation oriented language
Tinderbox	Source code compiling tester
Simul8	Specializes in discrete event simulation
Simulate First	Simulation software
SuperPro	Chemical and biological process design
UniSim	Plant simulation - design, optimization, engineering studies, operations
Vensim	System dynamics modeling software
Witness	Simulation software with GUI. General modeling, has versions for manufacturing and service/process performance

10.2. Appendix B: Supply Chain Analysis Dashboard

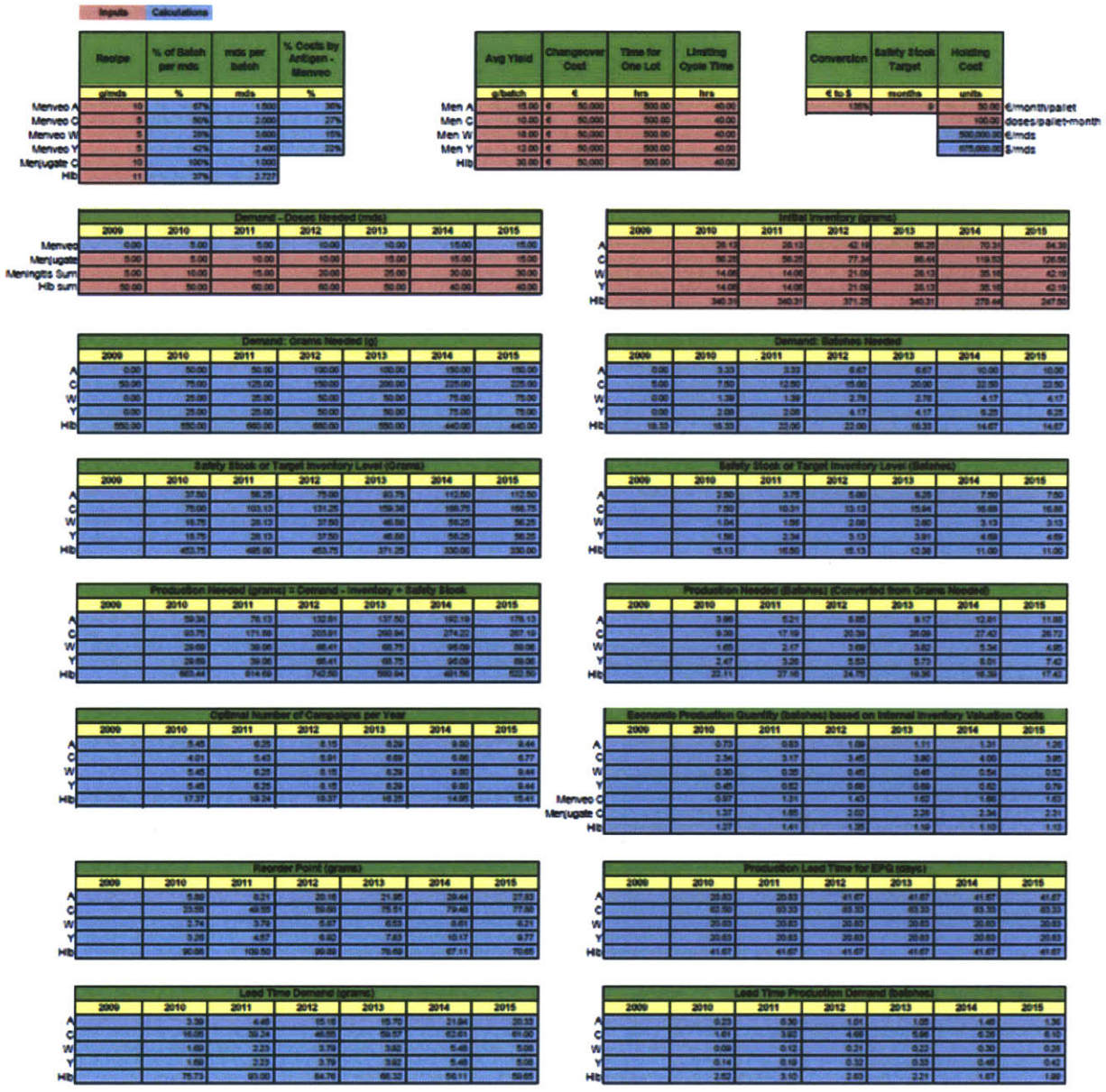

Figure 10-1 Supply Chain Analysis Dashboard