Development of Operations Based Long Range Network Capacity Planning Models

by

Cynthia M. Wilson

B.S., Chemical Engineering
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Submitted to the MIT Sloan School of Management and the
Department of Chemical Engineering
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ABSTRACT

Planning for vaccines manufacturing capacity is both a complex task requiring many inputs and an important function of manufacturers to ensure the supply of vaccines that prevent life-threatening illnesses. This thesis explores the development of an operations based long range capacity planning model to facilitate the annual strategic capacity planning review at Novartis Vaccines. This model was developed in conjunction with process owners at Novartis Vaccines and utilizes operations principles, non-linear optimization, and process data to efficiently calculate the capacity of the vaccine manufacturing network. The resulting network capacity is then compared to the long range demand for vaccine production to determine capacity deficits and surpluses in the current manufacturing network as well as analyzing options for more efficient capacity usage.

Although this model was developed specifically with respect to the Novartis Vaccines manufacturing network, the capacity calculation and gap analysis tools for single and multi-product facilities as well as batch allocation for in multi-product, multi-facility networks are also applicable to other companies and industries that utilize batch processing. The model was validated utilizing process information from a production line that was already operating near capacity and showed a 95% agreement with the data from this line. Additionally, this operations based planning model was able to achieve buy-in from both process owners and the global strategy organization allowing it to be implemented in the planning cycle. Use of this tool enables efficiency and transparency in capacity analysis as well as the tools to examine the impact of a range of scenarios on the manufacturing network.

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Table of Contents

Table of Figures

1 Introduction

1.1 Problem Statement

Long range capacity planning allows vaccine manufacturers to identify shortfalls in their available production capacity compared to the forecasted demand for the life saving vaccine products they manufacture. The long range time frame allows manufacturers to plan and execute capacity, regulatory, and third party manufacturing capacity adjustments as necessary based on demand. It also enables manufacturers to look forward and plan for the introduction of new products in the pipeline. The purpose of this thesis project is to develop a model that will allow Novartis Vaccines & Diagnostics to more efficiently balance commercial demand and production capacity in the two to five year timeframe.

1.2 Background and Motivation

Prior to this project, for 2-5 year (long range) global capacity planning, Novartis Vaccines primarily used a manual method of identifying shortfalls by matching available capacity, as identified by each facility, to the long range expected commercial demand. This manual method is resource intensive and involves redefining manufacturing capabilities for each product every year. The planning process usually involves limited interaction between planning for primary production (bulk vaccine components) and planning secondary production (vaccine formulation and filling) in allocating manufacturing capacity as well as in identifying methods to rectify capacity shortfalls. Additionally, examining the manufacturing network on an individual facility basis has the potential to lead to locally optimized manufacturing networks rather than a globally optimized supply chain (Simchi-Levi, Kaminsky and Simchi-Levi 2008).

Novartis Vaccines also lacked a standard definition for what assumptions are included capacity (or capability) calculations for vaccines manufacturing processes. This creates a variety of "capacity" definitions throughout the organization and results in a variety of different assumptions used in the capacities utilized for planning

1.3 Hypothesis

Operations principles and operational data can be used to calculate the capacity of both single product and multi-product vaccines manufacturing equipment, and these capacity calculations can be used to identify both capacity shortfalls and surpluses when compared to the commercial demand forecasts for each year.

1.4 Methodology

The methodology utilized in this project involves two phases. The first is the development of a standardized methodology to calculate the capacity of all of the process operations for Novartis Vaccines and Diagnostics. Secondly, the resulting capacities are compared against the forecasted commercial demand in the two to five year time horizon in a framework that allows analysis of both a base case as well as the ability to conduct scenario analysis of the capacity utilization effect of changes in various operational parameters.

1.4.1 Phase 1: Capacity Calculation

The initial capacity calculations are based on operations principles of identifying bottlenecks and calculating process yields based on these bottlenecks. The calculations are also adjusted to include a scheduling loss allowance for planned downtime and regulatory activities as well as

operating allowances for losses due to unplanned downtime and reject rate (based on operating experience and/or historical data).

The capacity calculation methodology for each primary and filling line has been validated with the process owner and tailored as necessary to fit the process using available data and guidance from process experts. Process data such as cycle time, turnover time, and yields were collected and/or validated by operations staff. For the current model, the formulation and packaging steps are assumed not to be bottlenecks and are not included in the model.

1.4.2 Phase 2: Long Range Planning Model

The long range planning model connects the commercial demand forecast with the production capacity. This model contains the linkages between final product demands, various locations and production lines where each product can be filled, vaccine components in each product, component production locations, and yield losses. Using the capacities calculated in Phase 1, this model identifies the capacity gaps and surpluses for each product, line, or production facility. Furthermore, this model allows planners to analyze the effects of changing operations parameters or conditions on the network capacity and expected utilization.

1.5 Results

Through thesis research at Novartis Vaccines facilities worldwide, a model based on operational principles has been developed to enable planners to balance supply and demand in the manufacturing network. The capacity model methodology was able to achieve a 95% agreement with the performance of the validation lines, which are considered to be running at capacity. Additionally, this long range planning model received the necessary buy-in from key process owners and is being to be used as part of the Novartis Vaccines planning process.

1.6 Thesis Overview

This thesis is organized into five chapters. The first chapter covers the introduction of the project and background. Chapter two provides some background into the importance and evolution of the vaccines industry and overview of Novartis Vaccines. This chapter also gives an introduction to the vaccine manufacturing process, regulatory control, and manufacturing challenges that impact model development. The third chapter details the development and formulation of both the capacity methodology and long range planning model. The fourth chapter gives the results of the project. Chapter fives details model recommendations and conclusions for Novartis Vaccines, as well as applications to other companies and industries. The variables that are utilized in this thesis and equations and their definitions are included as Appendix A. All figures and data contained in this thesis have been sanitized to protect the confidentiality of Novartis Vaccines data.

2 Vaccines Industry and Novartis Overview

The United States Department of Health and Human Services defines a vaccine as "a product of weakened or killed microorganism (bacterium or virus) given for the prevention or treatment of infectious diseases" (US HHS). The weakened or killed viruses or bacteria are called antigens, and they prevent diseases because when the immune system recognizes the antigens it begins to produce antibodies that are able to help the body provide resistance to the full form of the disease when exposed at a later time (Hoyt 2007).

2.1 Vaccines Development

The first major effective vaccine was developed in 1796 by Edward Jenner to prevent smallpox. Previous attempts at smallpox vaccinations had been attempted by injecting smallpox or inhaling smallpox scabs in an attempt to only get a mild case, but many people still died from this practice. Jenner observed that patients who developed non-life threatening cowpox from their exposure with cows did not develop the much more life threatening smallpox. Accordingly Jenner developed a vaccine that would give people a mild version of cowpox to protect them from smallpox. The term "vaccine" actually comes from this discovery. "Vacca" is the Latin word for cow and "vaccina" was the virus used in the smallpox vaccine. Louis Pasteur applied the term vaccine to all forms of prophylactic immunization beginning in 1881. In 1979, the World Health Organization declared smallpox to be completely eliminated (Kit 2007), (The Gale Encyclopedia of Science 2004).

In 1885, Louis Pasteur developed the first vaccine developed in a laboratory for rabies. The vaccine consisted of a weakened live virus from infected rabbits. As Pasteur continued his

development of the rabies vaccine, he discovered that the rabies virus produced a weakened (or attenuated) response in dogs when it had first been serially passed through rabbits. This development of the attenuated live virus was a significant step in developing a safer vaccine with lesser side effects. Live attenuated viruses can cause a mild form of the disease in a small number of people, but significant protection against the full strength antigen. Vaccines for polio, measles, rubella, mumps, yellow fever, influenza, and chickenpox are a selection of vaccines that are still given as live attenuated viruses today (Kit 2007), (The Gale Encyclopedia of Science 2004), (Hoyt 2007).

Pasteur continued his experiments with the rabies vaccine to also discover that the rabies virus could be "inactivated" by the chemical formalin so that it still caused an immune response but was not infectious. Eventually, this lead to the development of other "inactivated" or "killed" vaccines as well including vaccines for polio, mumps, influenza, Japanese encephalitis, and equine encephalitis (Kit 2007). Because the antigens are dead, inactivated vaccines do not carry the risk of developing a mild form of the diesase, but immunity from these vaccines generally declines over time and multiple doses are often required (Hoyt 2007).

Subsequently, other types of non-infectious vaccines have been developed including polysaccaride vaccines which contain only the polysaccaride coat of the virus linked to a carrier protein. Polysaccaride vaccines have been useful in combating Hemophilus influenza type b (HIB). Recombinant and subunit vaccines which are comprized of only the immunogenic viral proteins linked to adjuvants or formed into vesicles are also non-infectious vaccines. The lack of non immunogenic components limits the risk of exposure to infectious virus and adverse side effects. The hepatitis B vaccine has been developed using recombinant subunit vaccine

technology in recombinant yeast cells which contain the gene for the hepatitis B antigen (Kit 2007), (The Gale Encyclopedia of Science 2004).

As vaccine technology continues to advance a number of vaccine technologies are in development including vaccines using synthetic peptides, biosynthetic peptides, recombinant protiens, DNA, and genetic engineering. These technologies are being developed in an attempt to find safe and effective vaccines against a variety of diseases that kill at least 8 million people year including pneumoncoccal pneumonia, AIDS, malaria, acute respiratory infection and rotavirus.

Routine vaccination of children and adults has been highly effective in minimizing the morbidity associated with these diseases. Table 1 shows the advances that have been made in limiting morbidity in the United States for a selection of commonly vaccinated diseases.

Table 1: U.S. Morbidity Rate Selected Diseases

Disease	Maximum U.S. Morbidity		1998 U.S. Morbidity
	# of cases	Maximum Year	# of cases
Diphtheria	206,939	1921	1
Measles	894,134	1941	100
Mumps	152,209	1968	666
Pertussis	265,269	1934	7405
Polio	21,269	1952	1
Rubella	57,686	1969	364

Source: Kit 2007

However, despite the progress, world-wide approximately four million people die every year from vaccine preventable diseases including:

- Measles: 1,100,000 deaths
- Hepatitis B: 800,000 deaths

- Haemophilus influenzae type B (HIB): 500,000 deaths
- Tetanus: 500,000 deaths
- Pertussis (whooping cough): 350,000 deaths
- Rubella: 300,000 deaths
- Yellow fever: 30,000 deaths

Of these, children under five years old account for 1.4 million or 14% of the global mobidity for children under five (World Health Organization). These deaths occur partially because of the enormous challenge of vaccinating a global population, many of whom lack adequate healthcare. In the United States and many European countries, some parents have chosen not to vaccinate their children for safety, political, or religious reasons. This practice however, leaves their children exposed to the devestating consequences of contracting vaccine preventable diseases. During the U.S. measles epedimic of 1989, 18,000 people were infected. Even though the measles vaccine had been available in the United States since 1960, only 15% of those who contracted the disease had received a measles vaccine. Additionally, lack of proper (and recommended) vaccination for pertussis (whooping cough) for many children in the United States has resulted in approximately 30,000 American children per year contracting the disease (Kit 2007), (Alexandra & Markel 2005).

2.2 Major Players

As of the end of 2010, the vaccines industry is comprised of five major players: GlaxoSmithKline, Sanofi Aventis, Merck, Pfizer, and Novartis, and these five companies supply 80% of the global vaccines market. Over the past 10 years, the vaccines industry has seen market share consolidation as the number of major players decreased from fourteen in 1988 to these five players in 2010. The majority of the players that exited the industry during this period can be

attributed to the small margins for vaccine production, the cost of vaccine research and development, national vaccine policies, and liability concerns (Prifti).

Table 2: Top Five Global Vaccine Manufacturers

	GlaxoSmith Kline	Sanofi Pasteur	Merck	Pfizer (Wyeth)	Novartis Vaccines
Estimated 2009 Vaccines Revenue (million USD)	$ 5960	$ 5015	$ 3631	$ 3007	$ 2424
Cholera		x			
Diphtheria	x	x	x		x
Haemophilus influenza type B (HIB)	x	x	x	x	x
Hepatitis A	x	x	x		
Hepatitis B	x	x	x		
Herpes Zoster (Shingles)			x		
Human Papillomavirus (HPV or Cervical Cancer)	x		x		
Influenza (Seasonal and Pandemic)	x	x	x		x
Japanese Encephalitis		x			x
Measles	x	x	x		
Meningitis ACWY	x	x			x
Mumps	x	x	x		
Pertussis (Whooping Cough)	x	x			x
Pneumococcal infections	x	x	x	x	
Poliomyelitis (Polio)	x	x			x
Rabies		x			x
Rotavirus	x		x		
Rubella (German Measles)	x	x	x		
Tick Bourne Encephalitis (TBE)					x
Tetanus	x	x	x		x
Tuberculosis		x	x		
Typhoid	x	x			
Varicella	x	x	x		
Yellow Fever		x			

Sources: Merck, Sanofi Pasteur, GlaxoSmithKline, Pfizer Inc., Novartis, Center for Disease Control and Prevention

The next five vaccine manufacturers are much smaller in market share and focus either on a more narrow market or have only a few commercial products. They are as follows:

China National Biotechnology Corporation (CNBC): CNBC is the state owned biotechnology company in China which produces vaccines for thirteen diseases. CNBG enjoys a 80% market share for vaccines in China (DCVMN), (BioPharmaLink Profile).

Baxter International: Baxter is a global diversified healthcare company that manufactures vaccines for Tick Bourne Encephalitis, Meningitis C, and influenza (Baxter).

CSL Limited: The CSL Biotherapies division manufactures the seasonal influenza vaccine and acts as a third party distributor for other vaccine manufacturers in Australia and New Zealand (CSL).

Crucell: Crucell is focused on producing vaccines for influenza, hepatitis A, hepatitis B, typhoid fever, and cholera (Crucell).

Solvay: Solvay Biologicals, a division of Solvay Pharmaceuticals manufactures the seasonal influenza vaccine (Solvay 2010).

In 2002, Dr Robert Goldberg of the Center of Medical Progress at the Manhattan Institute described the pharmaceutical industry's view on vaccines as "a brackish backwater of other biotechnology and pharmaceutical enterprises" (Goldberg 2002), but more recently the vaccines industry has been undergoing a consolidation with global diversified healthcare companies. In 2004, Sanofi-Aventis acquired its vaccines division, Sanofi Pasteur as part of Sanofi-Synthélabo's acquisition of Aventis. Novartis AG's vaccines division, Novartis Vaccines and Diagnostics was formed with the acquisition of Chiron Corporation in 2006 (Novartis 2006), and Pfizer entered the vaccines market with the acquisition of Wyeth in 2009 (Pfizer 2009). At the end of 2010, Johnson and Johnson was in the process of acquiring vaccine manufacturer Crucell (Crucell 2010).

2.3 Regulatory Control

Like the rest of the pharmaceutical and biotechnology industry, the vaccines industry is highly regulated by the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMA) in the European Union, and many other regulatory bodies from other countries where the company's products are sold. The World Health Organization provides regulatory recommendations which are used by many national organizations. The quantity of regulatory bodies, variation in regulations from different countries, and intensity of scrutiny in both development and manufacturing of vaccines requires significant investment and effort put into compliance by vaccine developers and manufacturers (WHO 2011), (FDA 2010), (The College of Physicians of Philadelphia).

Government regulation of vaccines began in 1902 in the United States government passed a law that later became known as the "Biologics Control Act". This was the first government regulation on the quality of drugs and it established an agency to oversee biologics manufacturing facilities. Licensing for biologic products began in the U.S. in 1944 The Division of Biologic Standards, which later became part of the FDA, was formed in 1954.

During vaccine development, once promising vaccine candidates are identified and proven nontoxic in animals or cells, they must undergo a series of clinical trials in humans to prove their safety and efficacy. The vaccine material developed for these clinical trials must be manufactured in accordance Good Manufacturing Practices. Human clinical trial requirements vary slightly for each regulatory body, which sometimes requires different clinical trials to be conducted in different countries. However, they generally progress to approval in three phases:

Phase I: Safety, appropriate dosage range, and side effects are studied using a very small group of people (generally less than 100 people).

Phase II: Effectiveness, or efficacy, of the vaccine is studied in a larger group of people (generally hundreds of people) against a placebo. Safety, dosage, side effects, and method of delivery are also studied in this phase.

Phase III: Efficacy of the vaccine is studied in a very large group of people (generally several thousand people) against a placebo as well as against other vaccines for the disease already on the market. Safety and side effects also continue to be studied and the much larger study population gives an opportunity to recognize rare side effects from the vaccine.

Following successful completion of the Phase III clinical trial, the vaccine manufacturer files licensing documentation with the appropriate regulatory authorities in each country where the vaccine is to be marketed. In addition to product data for safety, efficacy, purity, and potency; inspection of the manufacturing facilities and regulatory review of the product labeling is generally required before approval is granted for most agencies. Upon approval from the regulatory bodies, the vaccine can be administered to the approved population (The College of Physicians of Philadelphia), (U.S. National Institutes of Health 2007), (FDA 2010).

Regulatory agencies continue to monitor the safety and efficacy of vaccines following regulatory approval through inspections of manufacturing facilities and optional phase IV clinical trials for pharmacovigilance or continuous monitoring of large populations that have taken the vaccine (FDA 2005). In the United States, the FDA and CDC have developed a reporting system called the Vaccine Adverse Event Reporting System, where anyone can report serious events following

vaccination. These reports are then investigated by the FDA and CDC. The FDA and CDC have also developed the Vaccine Safety Datalink where researchers perusing approved studies can access data about populations that have been vaccinated (The College of Physicians of Philadelphia).

In order to be compliant with regulatory standards, vaccine manufacturers are required to produce vaccines in accordance with current Good Manufacturing Practices (cGMP or GMP). These standards provide guidance to vaccine industry on the minimum requirements for quality production systems. The FDA, EMA, and other regulatory authorities inspect vaccines manufacturing facilities regularly to ensure compliance with these regulations. There are GMP standards for facility organization, personnel, training, facilities, process controls, equipment, process and equipment validation, cleaning and maintenance processes, laboratory controls, standard operating procedures, deviations, material handling, sampling, testing, record keeping, packaging, labeling, and warehousing (21 CFR 210), (21 CFR 211).

2.4 Vaccine Manufacturing Processes

The vaccine manufacturing process consists of two major processes: bulk manufacturing and fill/finish manufacturing.

2.4.1 Bulk Manufacturing

Bulk manufacturing, also called primary manufacturing, is the biological process of making the bulk antigens (or active drug substances), as well as vaccine components that facilitate immune response in some vaccines called adjuvants.

Novartis Vaccines primarily uses either egg-based, fermentation, or cell culture-based biological processes to manufacture vaccine antigens. Although the exact process and necessary equipment varies for each vaccine, the basic process steps for egg-based antigen production are: inoculation, incubation, harvest, inactivation, and purification/concentration. Similarly, for fermentation the steps would be: fermentation, harvest, inactivation, and purification and for cell culture the steps would be: seed preparation, cell expansion, cell culture, and harvest.

Although many bulk processes share some of the same steps, producing more than one vaccine on the same set of equipment depends on multi-product production not only being technically feasible, but also on the regulatory feasibility, and set up and change over validation between vaccines. Regulatory validation of production is required not only for the general process but also for each facility and line. Additionally, many bulk processes have substantially long cycle times and changeover times required between the production of each vaccine. Multi-product production would not only require downtime for cleaning, sterilization and other changeover activities, but also a significant ramp up period before the first bulk material from the next vaccine was completed. Consideration of these factors generally leads vaccine manufacturers to utilize specialized or dedicated bulk production facilities and suites, where either a single antigen is produced or each of the antigens for a multi-valent vaccine is produced in series on the same equipment. Where multiple vaccines are produced using the same bulk equipment, they are generally very similar and of the same production type (egg-based, bacterial fermentation, etc.) For example, flu production capacity is often used to produce multiple vaccines. All three strains of the northern hemisphere seasonal influenza vaccine are often produced in series on the same production line. When seasonal influenza production is completed, the same line is often used to

produce the southern hemisphere egg-based influenza vaccine or an influenza vaccine for pandemic stockpiling.

2.4.2 Fill/Finish Manufacturing

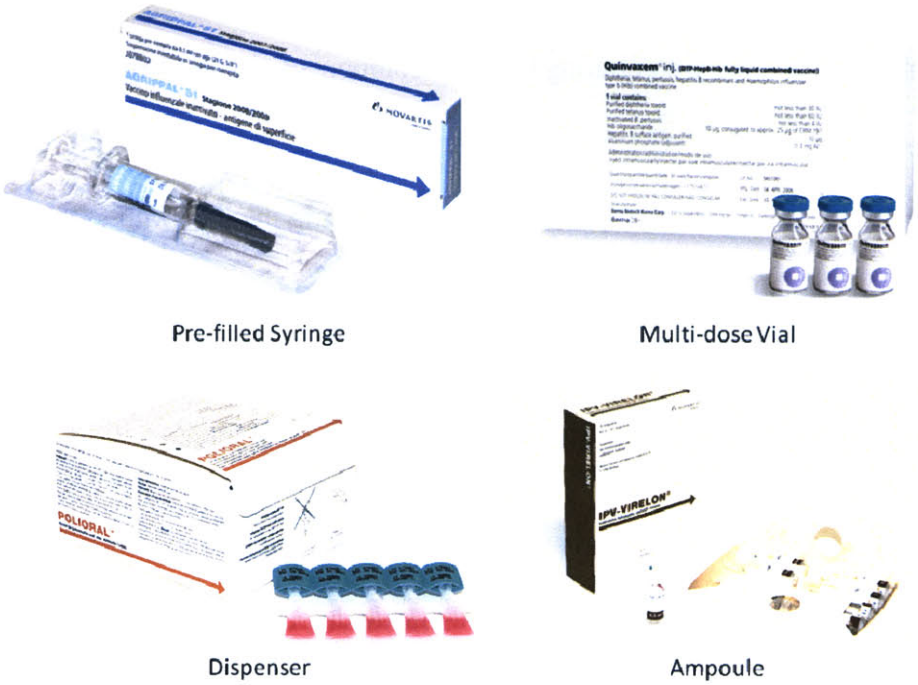
Fill/finish manufacturing, also known as secondary manufacturing, generally consists of three steps: formulating the vaccine by combining the bulk components in the correct amounts, filling the liquid vaccine into its final presentation form, and packaging. Packaging requires placing a label on container(s) of the vaccine components and then placing them as well as an information leaflet into a blister pack and/or box. For vaccines that need additional stability or shelf life, there is often an additional lyophilization, or freeze drying, step after filling that turns the liquid vaccine into a solid that has to be reconstituted just before administration.

There are a variety of presentation forms that vaccines can be filled into. The primary forms are pre-filled syringes and vials, although ampoules and plastic dispensers are also used for some products particularly in developing countries. Figure 1 depicts each of these presentation forms as well as a representative Novartis Vaccines product that is presented in that form for some markets. It is not uncommon for vaccines to be filled in different presentation forms for different markets depending on factors such healthcare provider's preference, economic advantages in each market, and regulatory constraints.

An additional layer of complexity for planning is that some vaccines require more than one presentation form to complete a single dose. Novartis Vaccine's meningococcal ACWY vaccine, Menveo, is an example of such a vaccine. The MenA component of the vaccine is a solid in a lyophilized vial, and the MenCWY components are in liquid form in a prefilled syringe or vial. Figure 2 shows an example of packaging for a single dose of this product, which contains a

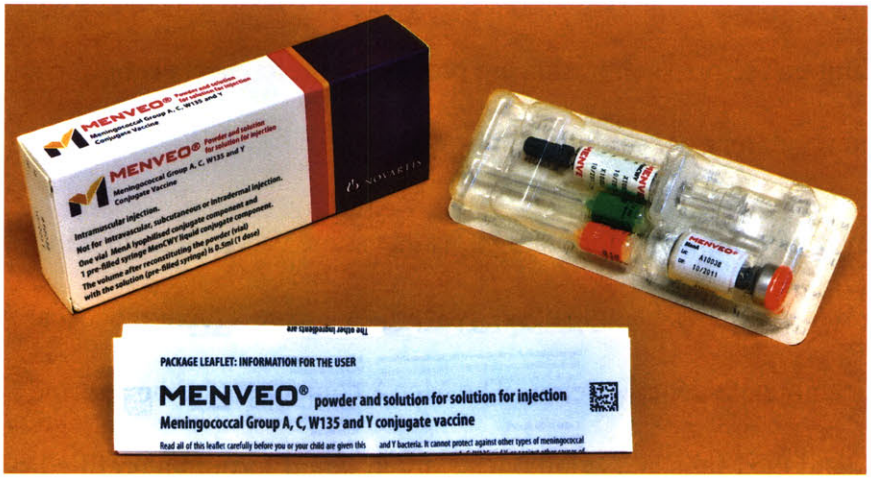
lyophilized vial, a pre-filled syringe, and two needles. Figure 2 shows the outer packaging for the product as well as the package leaflet that are both assembled as part of the packaging process.

Figure 1: Examples of Vaccines Presentation Forms



Source: Novartis Vaccines

Figure 2: Menveo Kit Presentation



Source: Novartis Vaccines

2.5 Challenges of Seasonal and Pandemic Flu Vaccine Production

2.5.1 About Influenza and Influenza Vaccines

Influenza, or flu, is a respiratory infection that affects 5-15 % of the American population each year during the winter months. The elderly and young children are most at risk for complications. On average 23,600 people die in the United States each year from flu related complications (CDC 2005).

Although the prevalent strains of influenza virus change from year to year, there are three main types of influenza virus that circulate in humans and some other animals: types A, B, and C. Type A is categorized into sub-types based on the presence of surface glycoproteins hemagglutinin (HA) and neuraminidase (NA). The naming convention uses the abbreviations H and N respectively each followed by number assigned to the type of glycoprotein present. For example, the recent "swine flu" epidemic was caused by a strain of the influenza A virus subtype H1N1 (CDC 2005).

2.5.2 Seasonal Flu Production

Most vaccine products are non-seasonal and have limited seasonal variability in a given year. However, the seasonal influenza (flu) vaccination is a highly seasonal product and an important part of the vaccines portfolio for many vaccines manufacturers. North America seasonal influenza epidemics typically occur during the late winter and early spring (Solvay 2010), (CDC 2005).

The seasonal influenza vaccine changes each year based on the strains of the flu vaccine that are expected to be circulating in that year. For northern hemisphere flu, the World Health

Organization selects the three strains of the flu virus to be used in the influenza vaccination for the upcoming season. These strains are released to vaccine manufacturers in February of each year. Generally two influenza A type and one influenza B type strains are selected (Emory Healthcare). Flu vaccine manufacturers then have until early fall when seasonal flu vaccinations begin to develop vaccines utilizing the recommended strains, undergo clinical trials for safety (in some markets), manufacture the antigens for all three strains, formulate the three antigens into a trivalent vaccine, fill into the final vial or pre-filled syringe presentation forms, package, and deliver the vaccines to distribution points. Because most vaccine manufacturers begin production "at risk" in January based on what they expect the strain selection to be, North American seasonal influenza vaccine primary manufacturing is limited from January to early fall of each year when there is no longer an economically viable market for additional product. Additionally, because the three strains for the vaccine are generally produced in series on the same equipment, the secondary manufacturing for the influenza vaccine operates in an even more limited season as it cannot begin until production lots of the third influenza strain begin to be released.

The seasonality of the influenza vaccine creates particular challenges in capacity and capability planning. Planners must consider the viability of either only operating the facilities part of the year, methods of producing other products in the off season to level-load the facility year round, or operating at a high level of utilization during the flu production season and a much lower level of utilization with other products during the off season.

2.5.3 Pandemic Flu Production

An influenza pandemic is generally caused by the emergence of a strain of the Influenza A virus that is significantly different than other circulating strains (CDC 2005). In 1918, there was an influenza pandemic that resulted in 40 million deaths worldwide (Solvay 2010). Pandemic

influenza vaccines are generally produced in the same method as the seasonal influenza vaccine, except that the antigen is produced for only one strain in the pandemic vaccine. When the pandemic influenza vaccine is required it is generally because of a pressing public health need and must be produced quickly and in large volumes to meet this need. In response to the avian and swine pandemic flu scares of the past few years, many countries have taken steps to reserve pandemic influenza manufacturing capacity and/or stockpile pandemic influenza vaccines. In turn, pandemic planning has affected how vaccine manufacturers plan influenza capacity based on incentives from these governments.

2.6 Novartis Company Background

2.6.1 Novartis Overview

Novartis AG is Swiss based company that seeks to provide healthcare solutions that address the evolving needs of patients and societies worldwide. Novartis had revenue of $44 billion in 2009 and a global reach in their four major divisions. The divisions: Pharmaceuticals, Sandoz (generics), Consumer Health, and Vaccines and Diagnostics represent a diverse portfolio of healthcare solutions for Novartis's customers (Novartis).

2.6.2 Novartis V&D Overview

Novartis' Vaccines and Diagnostics division (NVD) is the smallest but fastest growing of all the Novartis divisions. NVD posted revenues of $2.4 billion in 2009 with a growth rate of 13.9% over the previous year. Over 800 million vaccine doses are shipped annually to 85 countries resulting in a vaccine from Novartis providing potentially life-saving immunity to disease every 25 seconds (Novartis Vaccines).

2.6.2.1 Major Products

Novartis Vaccines produces vaccines for over 20 viral and bacterial diseases. It is the fifth largest producer of vaccines in the world and the second largest supplier of influenza vaccinations. Additionally, Novartis Vaccines produces Fluvirin, which is the second largest selling seasonal influenza vaccine in the United States. Novartis Vaccines produces vaccines in three product families: Flu, Meningitis, and Pediatric and Specialty vaccines. Table 3 gives a representative list and description of Novartis Vaccines products.

Table 3: Selected Novartis V&D Products

Product Type	Name	Indication Description
Flu	Agrippal (Agriflu)	Seasonal influenza (egg based)
	Fluvirin	Seasonal influenza (egg based)
	Fluad	Seasonal influenza (egg based) – adjuvanted
	Optaflu	Seasonal influenza (cell culture based)
	Aflunov	Pandemic adjuvanted avian flu (egg based)
	Celtura	Pandemic influenza (cell culture based)
	Focetria	Pandemic influenza (egg based)
Meningitis	Menjugate	Meningococcal C
	Menveo	Meningococcal ACWY
Pediatric, Specialty and Travel	Tetanol	Tetanus
	Td-Pur	Tetanus, diphtheria
	Vaxem Hib	Haemophilus influenza type B (HIB)
	Quattvaxem	Diphtheria, tetanus, pertussis, and HIB
	Quinvaxem	Diphtheria, tetanus, pertussis, HIB, and hepatitis B
	Polioral	Oral polio (OPV)
	Rabipur (RabAvert)	Rabies
	Encepur	Tickbourne Encephalitis
	Ixiaro	Japanese Encephalitis

Source: Novartis Vaccines

2.6.2.2 Sites

The global Novartis Vaccines manufacturing network currently spans six sites in five countries. Each site acts as a center of excellence for production of a particular type of vaccine, vaccine

component, or part of the vaccine manufacturing process. The global manufacturing network consists of facilities in:

- Liverpool, England – Egg-based flu vaccine production
- Marburg, Germany – Travel and pediatric bacterial vaccine production (Tetanus, Diphtheria, Pertussis, TBE, Rabies), Lyophilization
- Siena, Italy – Egg based flu vaccine production, Polio
- Rosia, Italy – Glycoconjugate bulk vaccine production, fill/finish and packaging
- Holly Springs, North Carolina USA – Flu Cell Culture bulk vaccine production, fill/finish and packaging
- Ankleshwar, India – Rabies vaccine production, fill/finish and packaging

Contract manufacturers also form a key component of the vaccines manufacturing network. These third parties provide an economic method of fulfilling peak demand periods or non-core components of the manufacturing process. Contract manufacturers are also able to consolidate demand for a particular type of technology that may be uneconomic at the volumes of individual producers, but the volumes from several producers allow them to achieve economies of scale unavailable to individual producers. Contract manufacturers primarily fulfill processes that are not intellectual property intensive such as fill/finish and packaging.

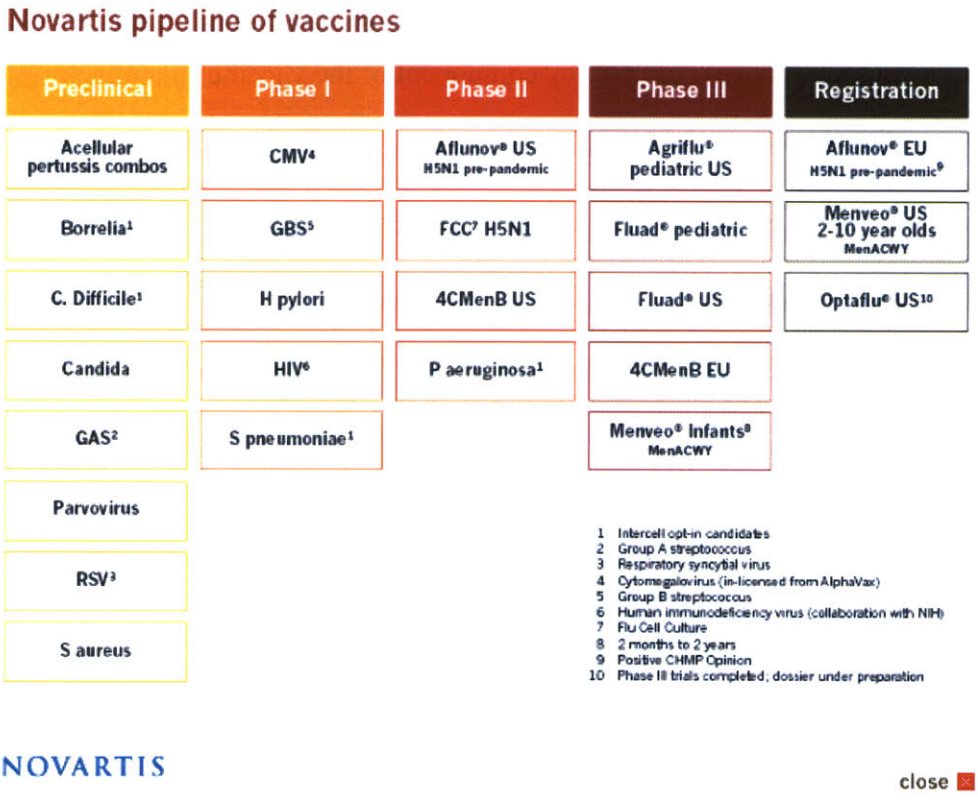
2.6.2.3 Novartis Vaccines Development

Novartis formed its Vaccines and Diagnostic division in 2006 with the $5.4 billion acquisition of Chiron. Chiron faced serious supply constraints and sterility problems. These resulted in the

shutdown of one of its production facilities by British regulators in 2005, which caused major shortages of the influenza vaccine. Novartis led the turnaround effort with aggressive management reorganization and growing the technical abilities of the organization. This turnaround enabled Novartis Vaccines to be a leading provider of the 2009-2010 H1N1 pandemic influenza vaccination and the first provider to achieve both European Union and United States regulatory approval for their pandemic vaccine (Staton 2010), (Bigelow 2010).

Looking forward, Novartis has a strong pipeline of vaccines in development as illustrated in Figure 3. The vaccines in development include a seasonal influenza vaccine produced in cell culture, approval of the meningitis ACWY vaccine for additional age groups, a four-valent meningitis B vaccine, group B streptococcus, H pylori, and HIV (Novartis Vaccines). Development of these vaccines and others like them will continue to further Novartis Vaccine's mission of disease prevention.

Figure 3: Novartis Vaccine Pipeline 2010



Source: Novartis Vaccines

3 Model Development

The Long Range Planning Model is a capacity analysis model that uses operations data and principles as well as non-linear optimization to calculate the capacity of each of the Novartis Vaccines manufacturing processes. This model is designed to facilitate decisions about the Novartis Vaccines manufacturing network design and product allocation. The model uses this capacity information as well as Novartis Vaccine's demand forecast to efficiently identify gaps between the demand and Novartis' capacity limited ability to supply. Positive gaps (more capacity than demand) either indicate potential for greater production of current products or potential locations to be considered for pipeline products. Negative gaps (more demand than capacity), indicate that strategic decisions will be needed on how to best fill these gaps.

3.1 Model Timeframe

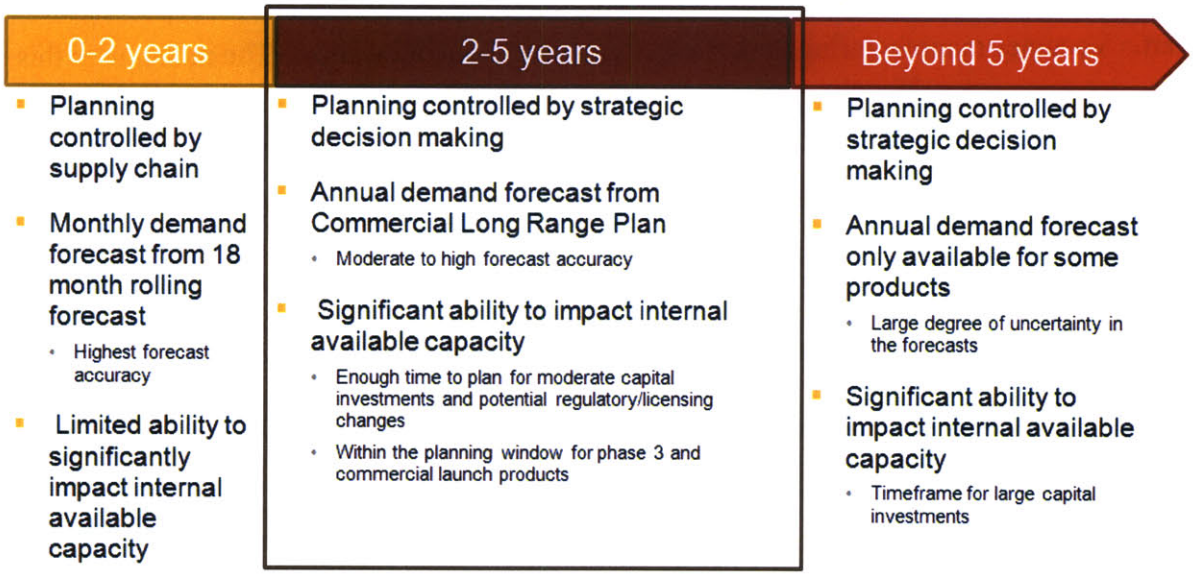
3.1.1 Timeframe Selection

The timeframe that was selected for the Long Range Planning Model is two to five years. This is the time period the best balances the need for accuracy in the product mix and forecasted demand with the need to act in advance of the demand or product launch to make capital investment or regulatory changes. Figure 4 details the factors in selecting a planning model time frame.

The two to five year planning period is the timeframe in which significant capital (Cohen and Roussel), staffing, or regulatory changes can be made to Novartis' internal capacity, but also a timeframe in which contract manufacturing capacity can be secured if necessary and the timeframe in which planning for phase III and commercial launch products takes place.

Additionally, planning for this time period is controlled by strategic decision making and this time period corresponds to the time period covered by the annual Commercial Long Range Plan.

Figure 4: Factors in Planning Model Timeframe



3.1.2 Timeline Implications on a Long Range Planning Model

Selecting a two to five year timeframe has specific implications on the assumptions used in the Long Range Planning Model. As a result, the validity of the outputs is limited to this timeframe.

3.1.2.1 Demand Risk Pooling and Lead Time

The demand forecast on which the Long Range Planning Model is based is an annualized forecast for each product. The Long Range Planning Model seeks to ensure that demand can be met on an annualized basis for strategic planning purposes rather than on a detailed weekly or monthly production schedule basis that would take into account order timing variability. However, in practice, there is variation in how much of each vaccine is in demand each month, and planning

for maximum capacity utilization does not give the flexibility to handle these variations and maintain the same service level (Simchi-Levi, Kaminsky and Simchi-Levi 2008).

As seasonal flu vaccines are a key part of Novartis' business and northern hemisphere flu must be produced in a limited time frame, both primary and secondary flu capacity has been considered by looking at "total" capacity, considering a 52 week year, and "seasonal" capacity which considers a shorter northern hemisphere flu vaccine production season.

Although short term supply chain constraints are generally not considered relevant to this model due to its forward looking nature, the annualized demand in the demand forecast is given based on the year in which the vaccine needs to be available to the customer. The vaccine must go through production, formulation, filling, and packaging. Each of these consumes production time, but there are also various forms of testing and required hold times at certain points in the process before the product can be released. As a result, the bulk vaccine manufacturing and filling need to happen substantially before the demand occurs. To account for this lead time in the model, the primary and secondary demand is backwards adjusted based on the lead time for each product. This process assumes a steady demand over the course of the year (except for influenza products), so that the primary production demand for a given year is approximately the year that it actually needs to be produced.

3.1.2.2 Staffing

Often facilities that do not have sufficient demand to operate at equipment capacity operate at staffing levels that are optimized for the current or expected near future demand. In these staffing constrained cases, staffing levels and shift schedules have a significant impact on the capability of the facility to produce product in the near term. Current staffing and shift scheduling may

continue to have a significant impact in the short term (zero to two years) as it takes a substantial amount of time to increase staffing levels because newly hired operators must often participate in a lengthy training and certification process. Therefore, for short term capability planning models (zero to two years) it is logical to include these factors. However, over the longer term (two to five years), staffing and shift structures can be changed to accommodate larger (or smaller) demands. Therefore, the capacity of the process equipment should govern long term strategic planning rather than current staffing levels or shift structures.

3.1.2.3 Inventory

Although margins of vaccine manufacturing are low relative to pharmaceuticals, vaccine manufacturers often face a competitive bid structure to provide government agencies with vaccines. The resulting demand can be highly variable as it depends on the outcome of the bidding process. Missing or delayed product delivery to customers due to production problems or lack of capacity can be devastating to company reputation and future business. In some cases, customers actually order vaccines from several companies and cancel orders from the companies with the longest lead times. Because of the high cost of losing a sale, both from the disease prevention perspective and from an economic perspective, the vaccine industry generally operates at very high inventory levels to reduce the possibility of shorting the market. However these products often must be managed in a cold chain and therefore have a high cost of storage. They are also products that have a defined shelf life, which can easily lead to costly inventory write downs if not carefully managed (Cohen and Roussel 2005).

Analysis of these inventory levels is beyond the scope of this model, but the Long Range Planning Model assumes that all processes are stable processes resulting in a constant average

level of inventory, such that the inventory level at the end of the year is the same as at the beginning of the year (Anupindi, Chopra and Deshmukh). Therefore, for each year only the demand level for that year needs to be produced. Neither utilizing safety stock nor stockpiling is considered for the capacity gap analysis, although these factors may be very useful in mitigating capacity shortages as they are identified in the model.

3.2 Capacity Model Overview

The capacity that the long range capacity model calculates is called the process capacity or practical operational capacity. This capacity is the annualized production potential, based on the maximum sustainable production rate of the process (Anupindi, Chopra and Deshmukh).

3.2.1 General Capacity Calculation Methodology

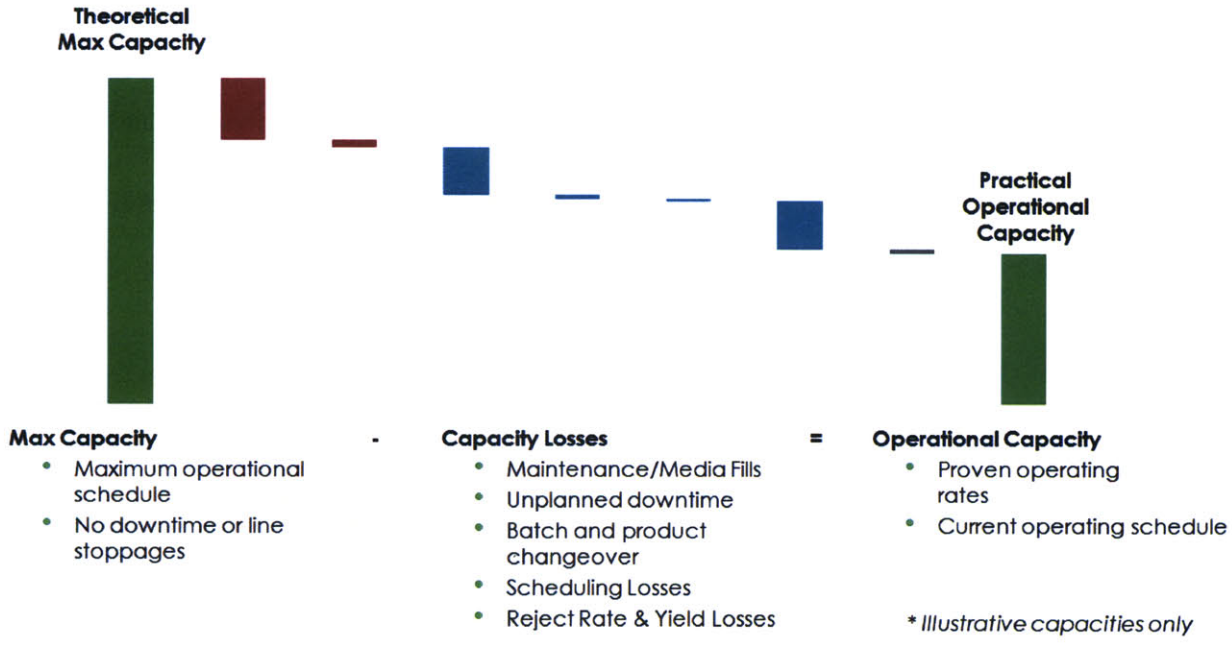
The long range capacity calculation methodology is an operations and optimization based approach to calculating vaccine manufacturing capacity. Both operations principles and non-linear mixed integer optimization programming is used to find the maximum theoretical capacity for each process as well as a practical operational capacity to be used for capacity planning.

The model calculations begin by considering the maximum theoretical capacity. This is the manufacturing capacity as limited by the process equipment. Under the maximum theoretical capacity assumption, the equipment operates twenty four hours a day, seven days a week, 365 days per year. The theoretical capacity is calculated by examining each of the processing steps and determining which step would produce the smallest amount of final product equivalents over the same period of time. This limiting step is defined as the bottleneck step, which sets the capacity for the entire process. The maximum theoretical capacity model explicitly excludes losses due to manufacturing defects, batch losses due to nonproductive biological conditions, and

other losses including: maintenance, regulatory activities, line stoppages, equipment changeover, cleaning and sanitization (Anupindi, Chopra and Deshmukh).

Once the maximum theoretical capacity case has been considered, the methodology acknowledges that it is unrealistic to operate a production facility in this manner, and therefore unproductive to utilize the maximum theoretical capacity for strategic planning. Both planned and systematic unplanned losses are part of the operating system and including them in the capacity calculation both improves accuracy of the capacity used in planning and assists decision makers in identifying high impact losses that can be targeted for future process improvement efforts. This process is illustrated in Figure 5.

Figure 5: Capacity Loss Analysis[1]



Some of the capacity losses are planned or required, such as planned maintenance downtime, media fills (for sterility testing), changeover and sterilization time between each batch and

[1] Capacities and losses are illustrative only

product produced on the same process, start-up time after shutdowns until product is produced again, and scheduling losses due to regulatory production limitations. Some losses considered are the result of manufacturing variability such as average reject rate, batch losses, and over fill, line rate loss, and average allowance for unplanned downtime including corrective maintenance and line stoppages. Once all of these losses have been subtracted from the maximum theoretical capacity, the resulting capacity is the practical operating capacity as shown in Figure 5.

The practical operating capacity is the capacity that planners can use to determine how much to expect a certain production facility to produce in a given year. The practical operating capacity is the capacity that among other factors considers regulatory restrictions, average batch yield, operating line speed, and makes an allowance based on historical data for unplanned downtime. The throughput of the process will be less than the practical operational capacity due to lack of or variation in demand, scheduling losses, and available workforce. As a result the following inequalities exist:

Theoretical Maximum Capacity $\geq$Practical Operational Capacity $\geq$Throughput

(Anupindi, Chopra and Deshmukh)

This methodology provides a robust approach to capacity calculation that can be applied to most of Novartis Vaccines processing units as well as many other batch processing units across both the vaccines and pharmaceutical industries and other industries. The limitation of this basic methodology is that it requires that all products produced on the same equipment have the same production characteristics and units of measure. Units of measure in this case can be defined quite broadly. The most useful unit of measure is the same unit of measure of the demand forecast (often doses), but other units of measure can be equally useful and can be converted

between doses of the demand forecast and production quantities. Units such as grams of active drug substance or other appropriate units like LF units for tetanus and diphtheria are useful in cases where many final products contain the same drug substance in different quantities. For multi-product facilities which produce products that do not share similar production characteristics, or where the common units approach is not sufficiently useful, a more complex capacity calculation methodology is required.

3.2.2 Multi-Product Facility Capacity Calculation Methodology

Facilities or processes that produce multiple products often have substantially different process characteristics like bottlenecks, cycle times, yields, or even process steps for each of the products. These processes require additional steps beyond the general capacity calculation methodology and are dependent on the product mix (Anupindi, Chopra and Deshmukh).

The one unit of measure that all processes with the same production characteristics have in common is the use of time and occupation of production vessels. This commonality can be exploited to allow the effective examination of multi-product facility capacities considering the products that will be required to be processed in each facility. In addition to process parameters, the capacity of these multi product facilities is also dependant on the regulatory approach to producing multiple products in the same facility. Two approaches will be considered in this section: product isolation by step and product isolation by product.

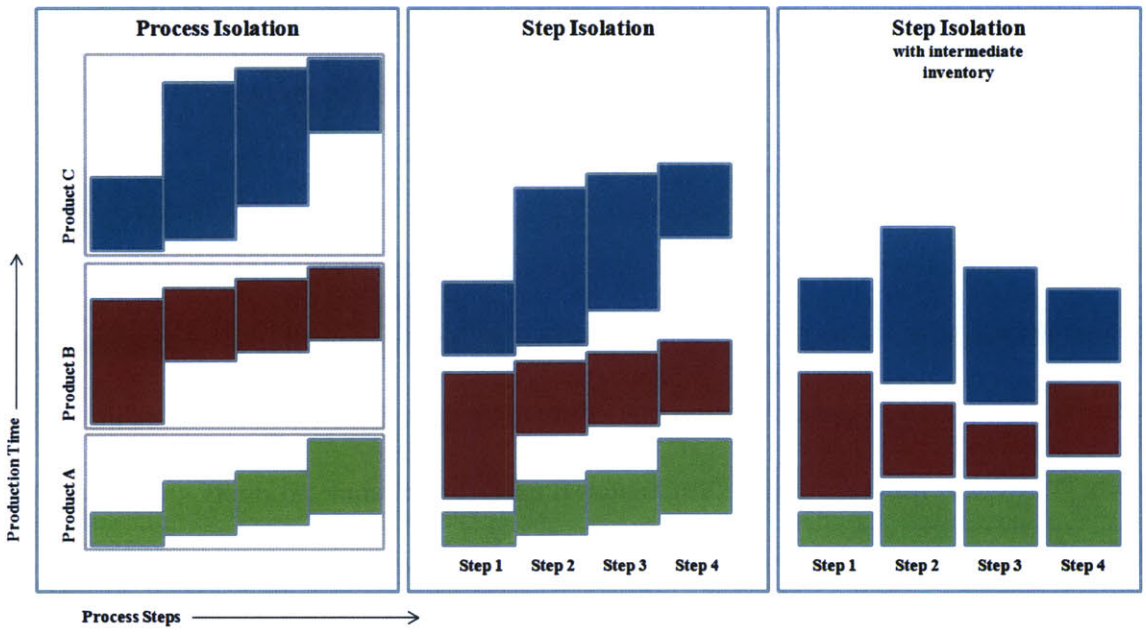
The multi-product capacity calculation methodology begins by carrying out the general capacity calculation methodology on each of the products that is produced in a facility separately. For example, if three products are produced in facility A, then the capacity of facility A would be calculated based only on producing product 1, then only product 2, and only product 3. The

exception to the general capacity methodology in this case is that the facility should consider the product changeover and start up for all the products in the process even though the capacity is only in terms of a single product. This will give the capacity of the process in terms of equivalents of each of the products produced on the line.

To further consider the impact of multiple products, it is necessary to understand the regulatory environment and constraints on process controls that processing multiple products places on the system. To prevent cross contamination that could take place from factors such as inadequate air handling controls or mishandling of drug material used for different products, there are often isolation procedures for upstream processes that prevent more than one product from being produced in the same area at the same time. Although there are many ways to isolate products within the system, this paper considers the two extremes: process isolation and step isolation. Process isolation is when the entire upstream production process is limited to producing one product at a time. Step isolation occurs when there are sufficient structural and/or process controls to sufficiently isolate each step so that multiple products can be processed in the same process but in different steps. Figure 6 illustrates how each of these constraints would affect product production scheduling and process capacity.

An important variation of the Step Isolation model occurs when there are sufficient stockpiles of intermediate inventory between process steps to allow the timing of each step in the production process to be decoupled from the previous and following steps. This model involves significant tradeoffs between process flexibility, utilization, and inventory holding costs. It also requires that that intermediates are sufficiently stable to allow for inventory holding. Analysis of these tradeoff factors is outside the scope of this paper. However, the capacity analysis will be considered in both the Step Isolation and Step Isolation with intermediate inventory cases.

Figure 6: Multi Product Production Methods



For each of the scenarios, it is assumed that the entire demand of each product is produced in one campaign in each year as this minimizes the amount of set up time required for each product and thus gives a best case examination of capacity utilization. However, there are trade-offs between the number of campaigns of each product and inventory holding costs due to scheduling and demand variability and distribution over the course of the year. As long term demand scenarios are annualized, examination of these factors is more suited to a short term planning analysis than to this model.

In all three of the models the capacity estimation methodology considered the mode of operation, demand for each year, and single product capacity analysis to determine how much of the process and/or step capacity is consumed by the demand for each product. Once this has been determined for each product, the sum of the utilizations either indicates a surplus of capacity or deficit. The surplus or deficit gap can be translated into equivalent doses of any product produced in the facility by considering the single product analysis.

3.2.2.1 Process Isolation

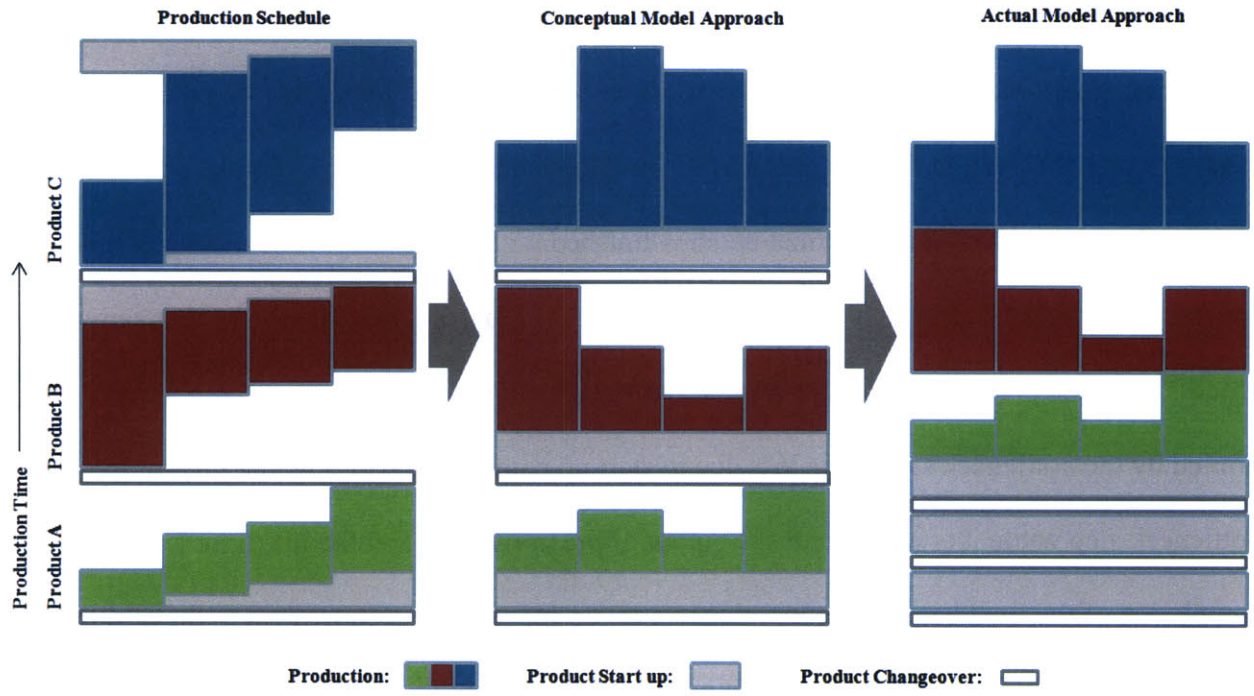
When the system lacks sufficient controls (process, HVAC, etc) to sufficiently isolate the individual steps so that more than one product can be produced at the same time (in different steps), production of the entire product must be completed before the production process can be changed over for the new product and production started on it. Figure 6 illustrates a graphical representation of a production schedule with the process isolation limitation.

In this case, there are additional losses that must be considered due to the fact that the bottleneck step must not only wait at the beginning of the process to receive material, it must also stand idle at the end of the process until the final batch is finished with its last step. The methodology for considering process isolation in a multi-product facility involves a loss due to the changeover process from the previous product, a productive loss due to process startup, and production limited by the bottleneck step. The loss due to start up compensates for the idle time of the bottleneck step while it is waiting for the output of previous steps and the idle time following the completion of the final batch. The loss due to start up for process is equivalent to the minimum time that it takes to complete one batch minus the cycle time of the bottleneck step. Figure 7 illustrates how the process isolation production schedule would look as compared to the methodology the model uses.

Conceptually, the model considers the product produced on the same line in series. However, in the model developed for the Long Range Planning Model all of the losses are considered first when examining the capacity in equivalent units of a single product and then that product's utilization of the rest of the capacity can be assessed as a percentage of remaining capacity for each year based on demand. This process is repeated for all products produced in this process. If the sum of all of the percentages of remaining capacity is greater than 100%, there is a production

deficit. If the sum of percentages is less than 100%, there is a production surplus. Both deficits and surpluses can be expressed in terms of any of the products on that process. In the process isolation methodology, if all of the products have the same bottleneck the result is the same as the step isolation method.

Figure 7: Process Isolation Methodology



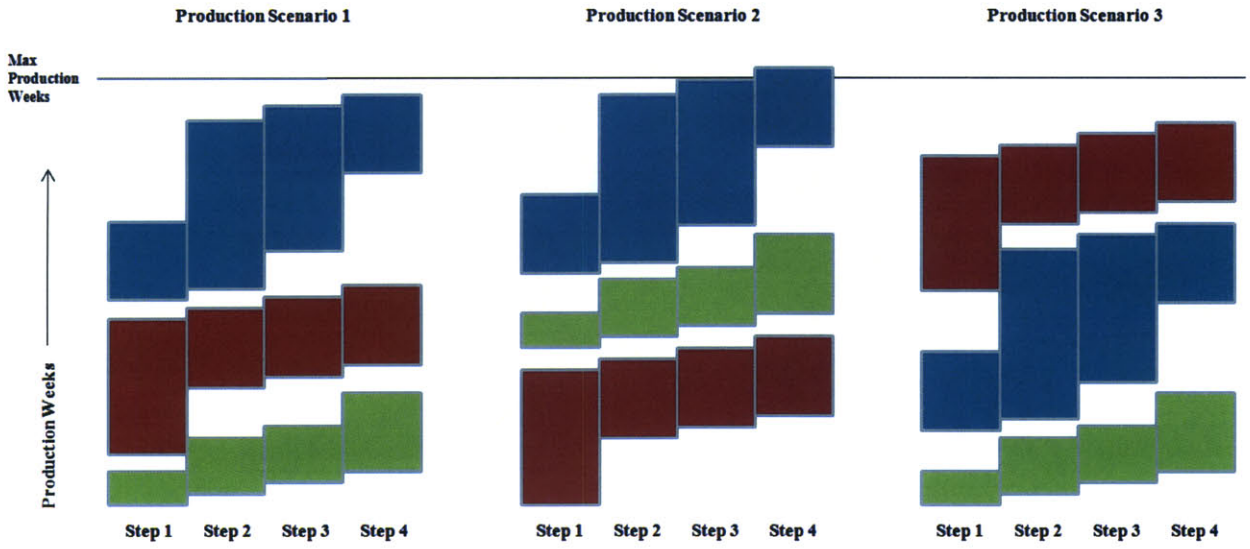
3.2.2.2 Step Isolation

Step isolation for multi-product facilities occurs when the production process contains sufficient controls so that production of multiple products can exist in the same production process at the same time, but are limited to different steps of the process. For the initial consideration of this case, no stockpiles of intermediate inventory stores will be held from previous or for subsequent campaigns of each product, therefore, all of the available material for the product in process must be completed before processing the next product on each step. It is also assumed that each step

will be run for the minimum time possible, which may create some temporary intermediate inventory if the previous process has a substantially longer cycle time per batch.

Because of the potential variation in cycle times for each step and product as well as variation in location of bottleneck steps for each product, the order that products are processed may substantially change the capability of the multi-product equipment. Figure 8 illustrates that as the process bottlenecks shift for each product, that scheduling downtime is created for all of the steps. In this case, scheduling optimization can be used to minimize downtime and maximize the amount of vaccine material that can be obtained out of the process.

Figure 8: Step Isolation Scheduling Effects

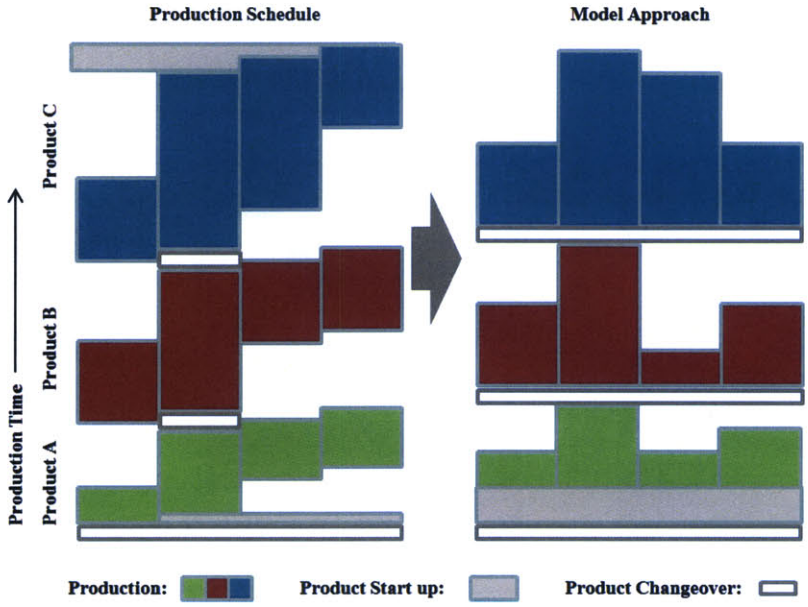


Although incorporating scheduling optimization was outside the scope of this project, the capacity model does consider a special case of step isolation in multi-product facilities. This special case occurs when all of the products produced on a particular process have the same limiting bottleneck step. This is not an unlikely scenario, because in the vaccines industry many

upstream processes are limited to producing in the same equipment vaccine components that are very similar and often simply different strains of the same disease.

When all the products have the same bottleneck step, the process is very similar to the process isolation methodology, but the model only needs to consider one product start up loss after annual maintenance, and then an additional product start up for every planned downtime when there will be no product in the system. Figure 9 illustrates both the production schedule for this special case of step isolation as well as the model methodology.

Figure 9: Step Isolation Methodology



3.2.2.3 Step Isolation with Inventory

Processes that stockpile sufficient stores of intermediate work-in-progress inventory for each of the products produced so that each step operates completely independent of each other and does not need to wait for the previous step for input material, can be considered and modeled using the Step Isolation with Inventory methodology. Because of the wealth of inventory, no start-up

losses are incurred because the final step can begin production immediately without waiting for material from the previous steps.

Additionally, each step is considered individually for all of the products produced using that step. After product changeover losses are considered for each step, each product's utilization of the rest of the capacity of that step can be assessed for each year based on demand. This process is repeated for all products and steps in the process. The sum of utilization of remaining capacity for each step reveals the step with the highest utilization. This indicates the limiting step for that combination of products in each year. Because the mix of products varies from year to year putting different amounts of pressure on the bottleneck step for each product the limiting step for the mix of products may change from year to year. If the sum of all of the percentages of remaining capacity is greater than 100% for the limiting step, there is a production deficit. If the sum of percentages is less than 100% for the limiting step, there is a production surplus. Both deficits and surpluses can be expressed in terms of any of the products produced on that step.

3.2.3 Multi-Product, Multi-Facility Decisions

In some cases, a single facility can produce multiple products, but a single product also has the ability to be produced in multiple facilities. It is often the case that each facility may have certain characteristics that will affect both its capacity and the network capacity based on the selection of products that are allocated to that process. This is especially true in secondary (fill finish) manufacturing in the vaccines industry. For example, a filling line that has no product changeover loss above the regular batch changeover loss, but has a slower line speed may be the best choice to run many low volume products. On the other hand, a line with a higher line speed, but a very long changeover time may be more appropriate to a few high volume products.

Regulatory restrictions also play a role. Products can only be run on lines that they are validated to be run on, and then they can only run for a validated length of time before the equipment operations must be stopped and the line sterilized. This validated run time limits the size of a batch for that particular product to the amount that can reliably be filled in that time window. Because of this, batch sizes vary not only from product to product on the same line, but also vary for the same product on different lines. The product batch size on a particular line affects the process capacity by impacting the amount of losses due to turnover between batches. Given the same product on two identical lines, but one with a small validated batch size and the other with a very large validated batch size, the large batch size will produce many more doses in the span of a year because of less time loss to changeover. Therefore, the allocation of products to different lines is important in determining capacity.

The optimal product allocation for a given year can be determined by using a non-linear optimization program in Excel Solver to determine which product allocation combination both meets demand for the year and minimizes downtime losses due to batch and product changeover, therefore, increasing total capacity potential. The details of this model are explored in the Model Formulation section of this paper.

3.3 Inputs and Outputs Overview

3.3.1 Model Inputs

Capacity calculation requires input data that is currently housed in a variety of sources around the organization principally: operations process owners, process improvement, planning, and supply chain. The model update design seeks to standardize what information is required from each

source and process, and where possible obtain the information from a consistent documentation location. Table 4 describes the information required and its source.

Table 4: Model Inputs and Sources

Information	Source Owner
Demand	Commercial Forecasting
Operational Assumptions / Data	Site Operations Process Owners
Process cycle times, Process success rates	Process Improvement Organization validated with Process Owners
Lead times	Supply Chain
Secondary Presentation Split	Current: Supply Chain Anticipated changes: Planning
Gross to Net Conversion Rate	Supply Chain or Process Owners

3.3.1.1 Demand

The commercial long range demand forecast is the source of all of the demand numbers for the Long Range Planning Model. This annually updated forecast provides two scenarios, which form the basis for analyzing the sufficiency of the presently available capacity.

3.3.1.2 Operational Assumptions / Data

A wide variety of data or operating assumptions are used in the calculation of each process capacity. Where possible, data has been used instead of assumptions in the model. The data or assumptions included in the capacity calculation and the variables assigned to them include:

Variable	Name	Description
H_D	Maximum hours per day	24 hours
D_W	Operating days per week	7 days
W_Y	Maximum weeks per year	52 weeks
W_{Sp}	Weeks of Seasonal Production	Weeks of production for seasonal influenza production on process "p"
W_{Mp}	Weeks of Maintenance	Weeks of annual scheduled maintenance on process "p"
W_{Rp}	Weeks of Ramp Up after Shutdown	Weeks of time required after process start up to start out putting product again on process "p"
W_{Fp}	Weeks of Media Fill	Weeks of non-productive processing due to regulatory

		sterility testing on process "p"
F_{Up}	Uptime Planning factor	Percentage of available time not impacted by unplanned down time on process "p"
F_{Dp}	Downtime Planning factor	Percentage of available time impacted by unplanned down time such as line stoppages and corrective maintenance on process "p"
R_{Sp}	Line Rate (Secondary)	Production rate in units/min on process "p"
B_{Lp}	Batch size	Batch size in million doses (or million dose equivalents) for product "i" on process "p"
F_{yip}	Batch yield	Percentage yield of the initial batch size for product "i" on process "p"
F_{Sip}	Batch success rate	Percentage of initial batches that successfully grow product within specification for product "i" on process "p"
H_{Bip}	Batch Changeover time	Hours required to clean, sterilize, and set up for the next batch between batches for product "i" on process "p"
H_{Cip}	Product Changeover time	Hours required to clean, sterilize, and set up for the next product after product "i" on process "p"
H_{Zjip}	Cycle Time	Hours that one batch of product "i" is required to occupy the process vessel(s) for step "j" in process "p"
H_{Tijp}	Takt Times	Hours of process time after one batch starts until the next batch begins for product "i" on step "j" in process "p"

Due to the standardization present in the model, most of the processes use the same set of data and assumptions to calculate capacity. However, due to special constraints or process differences in some processes there are additional data needs.

3.3.1.3 Process Cycle and Takt Times

While all of the input information is important, using the process cycle times to calculate the takt times is the most critical piece of information in determining capacity.

Cycle time (H_{zijp}) is the amount of time that a process step is occupied with activities related to a particular batch. This includes processing time (H_{Tijp}) and a set of activities collectively called batch changeover time (H_{Bijp}) which includes cleaning, sterilization, and set up for the next batch (Equation 1).

$$\forall\, ijp,\quad H_{zijp} = H_{Tijp} + H_{Bijp} \qquad \text{Equation 1}$$

Takt time (H_{Tijp}) indicates how frequently a new batch can be started. The easiest way to calculate takt time is to determine the cycle time and divide by the number of batches that could be on going at the same time (B_{Sijp}) as given in equation 2.

$$\forall\, ijp,\quad H_{Tijp} = \frac{H_{Zijp}}{B_{Sijp}} \qquad \text{Equation 2}$$

For example, if the cycle time for fermentation of Product A is 7 days for one fermentation, but there are 3 fermentation vessels so the takt time is: (7*24)/3 = 56 hours. When determining batch yield for each step (doses per lot), the batch or lot size must be defined the same way as it was for calculating the cycle time for that step.

3.3.1.4 Lead Times

The demand forecast is an annual two to five year forecast and is given in terms of the year that the vaccine needs to be ready to be delivered to the customer. However, because of the amount of time required to produce, formulate, fill, and package the vaccines, as well as the amount of delay caused by release testing at various stages of the process, production of the vaccine must start substantially before the customer actually demands it.

The lead times allow the model to adjust the commercial demand forecast back to the year where it would actually need to be produced and filled (assuming uniform demand over a year). The two lead times of importance for this model are:

- Primary lead time (P_{LT}): minimum time in months required from end of bulk production to final product release

- Secondary lead time (S_{LT}): minimum time in months required from filling to final product release

In the model, the adjusted demands are referred to as Primary Demand and Secondary Demand Equation 3 gives the demand adjustment equation for primary demand as an example assuming that lead times are less than 12 months.

$$P_{Diy} = D_{iy} *(12-P_{LT})/12 + D_{i(y+1)} *(P_{LT}/12) \quad \text{Equation 3}$$

3.3.1.5 Secondary Presentation Split

Novartis Vaccines has several products that it provides in multiple secondary presentations such as pre-filled syringe, vial, lyophilized vial, or ampoule. For the products with multiple presentations, the proportion of the demand that will be filled in each form is a key factor in determining the utilization of secondary capacity. The initial product splits are determined by the current product mix and modified by any planned changes in presentation format.

3.3.1.6 Gross to Net Conversion Rate

During primary production, the number of doses (or yield) that can be produced based on the bulk output of the primary production batch is called the gross yield. However, this yield does not consider losses due to secondary processes or overfill and the combination of the two often adds up to upwards of 30% loss. Net yield is the number of doses that can be obtained after these losses are considered. The Gross to Net Conversion Rate refers to this percentage of secondary loss and overfill that enables the accurate estimation of the number of doses that could actually be delivered to a customer. The Gross to Net conversion rate is used at the end of every primary capacity calculation to adjust the capacity to reflect the number of net doses.

3.3.2 Model Outputs

The output of the Long Range Planning Model displays process capacities, process demands, utilizations, and the capacity gap for the two to five year planning period. This data is provided in both numerical and graphical format to assist decision makers with planning. Figures 10 and 11 give an example of the Primary Model output for three example processes.

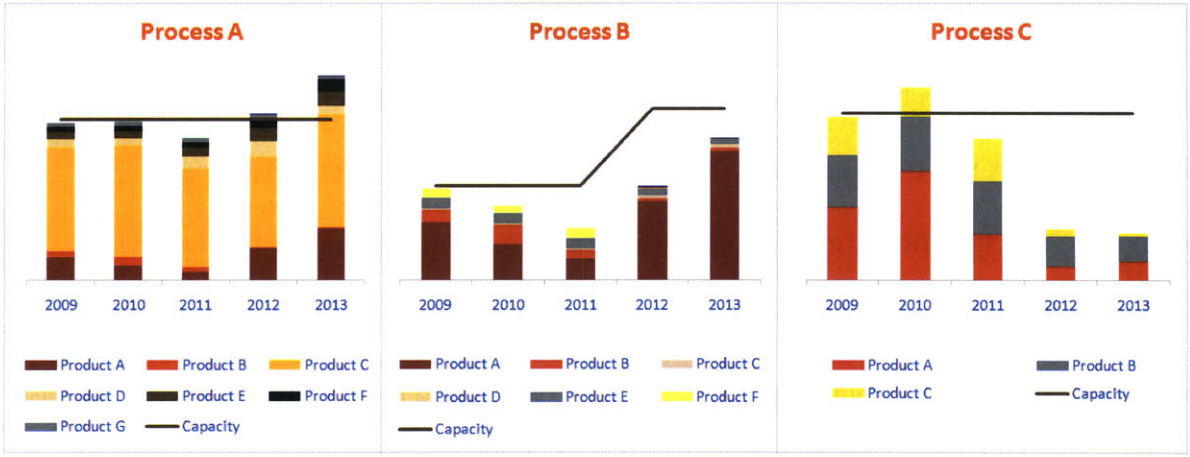
Figure 10: Primary Summary Quantitative Example[2]

Primary Capacity vs Demand		2011	2012	2013	2014	2015
Process A	Capacity (units)	1870	1870	1870	1870	1870
	Demand (units)	1864	1872	1695	1926	2370
Process B	Capacity (units)	1100	1100	1100	2000	2000
	Demand (units)	1056	859	603	1078	1647
Process C	Capacity (units)	700	700	700	700	700
	Demand (units)	681	806	591	211	196

Primary Utilization					
Process A	99.7%	100.1%	90.6%	103.0%	126.7%
Process B	96.0%	78.1%	54.9%	53.9%	82.4%
Process C	97.3%	115.2%	84.4%	30.1%	28.0%

Primary Capacity Gaps (mds)		2011	2012	2013	2014	2015
Process A	units	0.7	-0.2	21.5	-6.9	-61.5
Process B	units	0.5	24.7	56.2	113.4	43.4
Process C	units	2.3	-13.1	13.5	60.2	62.0

Figure 11: Primary Capacity Graphical Example[3]



[2] Data are illustrative only and do not reflect Novartis Vaccines parameters

[3] Figures are illustrative only

3.4 General Capacity Model Formulation

The primary goal of the capacity model is to calculate the practical operational capacity for each process by considering the maximum production potential and the operational losses incurred.

Effective Available Weeks (W_{Apy}) is the number of weeks that the process is available to produce product. It is calculated for each year, as shown in equation 4, by considering the Maximum weeks per year (W_Y) and considering the weeks of losses that come from planned maintenance (W_{Mpy}), media fills (W_{Fpy}), ramp up after shutdown (W_{Rpy}), planned project downtime (W_{Cpy}), and an uptime planning factor (F_{Up}). The calculation of the uptime planning factor is given as one minus the percentage of available time impacted by unplanned downtime (F_{Dp}) such as line stoppages and corrective maintenance (Equation 5).

$$\forall y,p,\ W_{Apy} = (W_Y - (W_{Mpy} + W_{Fpy} + W_{Rpy} + W_{Cpy})) * F_{Up} \qquad \text{Equation 4}$$

$$F_{Up} = 1 - F_{Dp} \qquad \text{Equation 5}$$

The next step in calculating the practical operational capacity is to examine the production process. For each step in the process the takt time of that step, as given in Equation 1, indicates how often a new batch can be started on that step in a sustainable manner. From a long range planning perspective, this takt time data is calculated based on equipment capacity and processing time and specifically eliminating workforce constraints. The effective number of batches that can be produced per week (B_{Wijp}) on each step is given by dividing available hours per week by the takt time for each step (Equation 6). For the long range planning model the base assumption for hours per week is 24 hours per day and seven days of operations per week.

$$\forall \text{ i,j,p, } B_{Wijp} = \frac{H_D * D_W}{H_{Tijp}} \qquad \text{Equation 6}$$

If the 24 hours a day, seven days a week operations model is not the short term operational model, it is expected that facilities could be ramped up to this level if necessary in the zero to two year time frame. There are some cases where a lower assumption would be appropriate, such as in cases where law or union contracts forbid operating on this schedule.

The number of effective batches per week is then multiplied by the effective number of weeks per year from Equation 4 to give the practical operational production step capacity in batches (B_{Nijp})for each product on each step of the process (Equation 7). The practical

$$\forall p,i,j, \; B_{Nijp} = W_{Apy} * B_{Wijp} \qquad \text{Equation 7}$$

operational step capacity is much easier to compare to demand when examined in demand equivalent units. Generally for vaccines the demand equivalent unit is in million doses. The conversion to practical operational step capacity in doses (C_{ijp}) (Equation 8) is achieved by multiplying by the average number of expected doses per batch (B_{Aijp}). The average number

$$\forall p,i,j, \; C_{ijp} = B_{Nijp} * B_{Aijp} \qquad \text{Equation 8}$$

of expected does per batch can be calculated directly from operations data for the process. However, from a loss analysis calculation perspective, if the relevant data is available it is useful to consider the losses assumed when average number of expected does per batch is used. Average number of expected doses per batch (B_{Aijp}) is calculated by considering the theoretical doses per batch (B_{Tijp}) and the yield losses due to both process yield loss (L_{Yijp}) which is the percentage of the theoretical yield of active drug substance in each batch that is unable to be recovered at the end of the process and batch loss (L_{Bip}) which is the percentage of process

batches that fail to grow (Equation 9). Because each step of the process may define the concept of "batch" differently it is important that batch size or yields are consistent for each process step with the definition of "batch" that was used for determining the cycle time for each step.

$$\forall p,i,j,\ B_{Aijp} = B_{Tijp} * L_{Yijp} * L_{Bip} \qquad \text{Equation 9}$$

Once the practical operational step capacity is determined for all the steps in the process, the bottleneck step and therefore the process practical operational capacity can be determined. The step capacity of the bottleneck (C_{Bpi}) is the minimum step capacity of all of the process steps in demand equivalent units (Equation 10). The practical operational process capacity (C_{Pi}) is limited by the step capacity of the bottleneck.

$$\forall p,i\ ,\ C_{Bpi} = \text{Min}(C_{ijp}) = C_{Pi} \qquad \text{Equation 10}$$

3.5 Capacity Model Formulation Variations for Complex Cases

3.5.1 Multi-product Facilities

The model formulation for multi-product facilities uses the general capacity model as its base, but utilizes the capacity analysis based on each product produced on the process to consider the utilization based on the demand mix for a given year.

3.5.1.1 Process Isolation

For multi-product facilities that practice process isolation, the model development begins with calculating the capacity based on the general methodology assuming that each product is the only one produced on that line. Secondly the capacity methodology is modified to account for additional losses due to producing multiple products, and then examine the fraction of available capacity that must be allocated to products within the demand.

The required changes to the base capacity model are primarily due to the fact that sharing equipment with multiple products, the system incurs additional losses due to multiple start up times and product changeovers. The available production week equation (Equation 4), is adjusted by subtracting weeks of product changeover (W_{Dpy}) as defined in Equation 12 and multiplying the weeks of ramp up after shutdown (W_{Rpy}) by the number of products produced in that process (N_{py}) the resulting equation is given in Equation 11.

$$\forall y,p,\ W_{Apy} = (W_Y - (W_{Mpy}+W_{Fpy}+W_{Rpy}*N_{py}+W_{Cpy}+W_{Dpy})) * F_{Up} \qquad \text{Equation 11}$$

$$\forall y,p,\ W_{Dpy} = \frac{H_{Cp} * N_{py}}{H_D * D_W} \qquad \text{Equation 12}$$

Making these adjustments to the general capacity model results in the calculation of the practical available capacity based on production of only one product, as if that product was produced on the same production schedule as the many products produced in the facility. In order to consider the effect of multiple products produced in the facility, the demand for each of the products must be considered. For a given year and process, the percentage of practical available capacity required to meet the demand is calculated for each product. The percentage sum of the all of the fractional capacities indicates the portion of the practical available capacity and also the portion of the available production weeks that are required to meet demand for the year. If the percentages sum to less than 100%, there is a capacity surplus. A sum of fractional capacity percentages greater than 100% indicates a capacity shortfall. The percentage of shortfall or

surplus can be analyzed as a percentage or converted into units of any of the products produced on that process by multiplying by the practical available capacity for that product.

3.5.1.2 Step Isolation

In both the Step Isolation with Inventory models and the special case of the Step Isolation model where all the products have the same bottleneck step on the process, the same formulation as the Process Isolation formulation is used except that the Available Production Weeks equation (Equation 11) is modified to fit the assumptions of each case. Specifically, the treatment of the ramp up after shut down (W_{Rpy}) is different in each case. In the Process Isolation case, the ramp up after shutdown was multiplied by the number of products. For the special case of the Step Isolation model, only one ramp-up is required after the annual maintenance (Equation 13), and in the Step Isolation with inventory case the intermediate inventory makes it unnecessary to consider ramp-up time (Equation 14).

$$\forall y,p,\ W_{Apy} = (W_Y - (W_{Mpy}+W_{Fpy}+W_{Rpy}+W_{Cpy}+W_{Dpy})) * F_{Up} \qquad \text{Equation 13}$$

$$\forall y,p,\ W_{Apy} = (W_Y - (W_{Mpy}+W_{Fpy}+W_{Rpy}+W_{Cpy}+W_{Dpy})) * F_{Up} \qquad \text{Equation 14}$$

Utilizing the appropriately calculated weeks of available production, the practical available capacities of each process can be calculated using the general capacity methodology. The multi-product analysis is subsequently carried out utilizing a similar percentage fractional capacity method as the Process Isolation method. However, in the step isolation case the sum of percentage utilizations for each process step must be considered individually. The step with the highest total utilization indicates the bottleneck and therefore the process capacity.

In utilizing the step isolation with inventory process, different products may have different bottlenecks on the same process. This methodology calculates the overall bottleneck for the entire year based on the demands for products produced on each process. As the proportions of each product demand change it is possible that the process bottleneck changes from year to year.

3.5.2 Multi-product, Multi-facility Capacities and Decisions

In situations where products can be produced in multiple facilities that also produce multiple products; the allocation of products to facilities is important in optimizing the utilization of capacity. A non-linear optimization program in Excel Solver is used to allocate batches of product demand to each of the production lines to both utilize production capacity efficiently and supply the demand (Anupindi, Chopra and Deshmukh). The capacity models that use the multi-product facility formulation are utilized as part of the optimization model. The capacity models provide input to the optimization and the outputs of the optimization model are utilized in the capacity model. The objective function of this model is to minimize the total amount of required down time on internal capacity due to batch changeovers (H_{Bpy}) and product changeovers (H_{Cpy}) and minimize the number of batches allocated to external capacity (B_{NiEy}). To accomplish this, the number of external batches is multiplied by a scaling factor (F_s) in hours per batch, which is slightly greater than the largest batch changeover time plus the largest product changeover time. This scaling factor incentivizes the model to prioritize product allocation to internal capacity rather than external capacity.

Objective Function: $\forall y$, Minimize $(\sum_{p} H_{Bpy} + H_{Cpy} + F_s * B_{NiEy})$ (Equation 15)

Decision variables and constraints of the optimization model are detailed as follows:

Decision Variables: B_{Nipy} = batches of product "i" produced on process "p" in year "y"

B_{NiEy} = batches of product "i" produced on external process "E" in year "y"

Constraints:

$\forall$ y,i, $D_{iy} = S_{iy}$ — For each year product and year, supply must equal demand (Equation 16)

$\forall$ y, $T_{Upy} \leq T_{Apy}$ — For each year, time utilized for processing, turnover, and downtime must be less than or equal to total time available (Equation 17)

$\forall$ y, $B_{Nipy} \geq 0$ — For each year, the number of batches of product "i" on process "p" must be greater than or equal to zero (Equation 18)

Where:

$\forall$ i,y $B_{Nipy} * B_{Sipy} = S_{ipy}$ — For each product and year, the number of batches of product "i" on process "p" times the batch size of product "i" on process "p" equals the supply of product "i" produced on process "p" (Equation 19).

$\forall i, y \quad \sum_{p} (S_{ipy}) = S_i$ — For each product and year, the sum across all of the lines of the supplies of a given produce equals the total supply for that product (Equation 20).

$\forall$ p,y, $T_{Apy} = W_{Apy} * D_W * H_D$ — For each process or year, the available production time is equivalent to weeks available calculated from Equations 4,11,13, or 14 and converted to hours (Equation 21).

$\forall$ p,y, $T_{Upy} = H_{Tpy} + H_{Bpy} + H_{Cpy}$ — For each process and year, the time utilized for processing is the sum of total annual batch processing, batch changeover, and product changeover time (Equation 22).

$\forall$ y, p, $H_{Tpy} = \frac{\sum_{i} (S_{ipy})}{R_{sp}}$ — For each process and year, the total annual batch processing time is the sum of all the doses of products that are produced on the line divided by the batch processing time (Equation 23).

$\forall$ y, p, $H_{Bpy} = \sum_{i} (B_{Nipy} * H_{Bip})$ — For each process and year, the total annual batch changeover time is the sum of all the number of batches of each product times the

batch changeover time for those liens and products (Equation 24).

$\forall$ y, p, $H_{Cpy} = \sum_{i}(B_{Nipy})$ *H_{Cip}

For each process and year, the total annual batch processing changeover time is the sum of all the number of batches of each product times the batch changeover time for those lines and products (Equation 25).

3.5.3 Influenza Vaccine Manufacturing

Production of influenza vaccine has two very distinct complications that warrant model adaptations in the long range planning model. First, because the market for North American flu vaccine is highly seasonal and the product itself is different from year to year, production must happen within a very limited timeframe. Secondly, because the flu vaccine contains three different strains and each of these strains produces widely different batch yields it is useful to consider the effects of the strain yield variability on capacity.

Weeks of Seasonal Production (W_L) is a user input to the model that indicates the maximum number of weeks of production time in either primary or secondary production that can be dedicated to seasonal product production. This variable is used in the weeks of available production equation (Equation 4) is used in place of the maximum number of weeks per year (W_Y). It is also assumed that planned maintenance and other planned down downtime are not scheduled during this peak production time and therefore these factors and the ramp-up time after shutdown during the peak production period is zero. The resulting equation for available weeks of seasonal production is given in Equation 26. When calculating influenza vaccine manufacturing capacity, both the annual and seasonal capacity should be calculated.

$\forall y,p,\ W_{Spy} = W_{Lpy} * F_{Up}$ Equation 26

Equation 26 should be used in place of the available weeks production equation (Equations 4,11,13, or 14) in the regular or multi-product capacity calculation methods. Because of the significant time constraints on the flu production season, manufacturers generally strive to produce each strain of the vaccine in a single campaign with the three strains being produced in series. Minimization of the number of campaigns minimizes capacity losses due to product changeover downtime.

Because influenza vaccine manufacturing can have a large variability in yield from strain to strain, it is useful to consider high, medium, and low yield cases. The middle case is defined as the expected value, the high case as the expected value plus one standard error, and the low case as the expected value minus one standard error of the yield. The expected value and standard deviations are calculated based on historical batch yields from the influenza vaccination strains that have been selected for the historical selection of years for which data is available and the vaccine has been produced in the current process. In a given year, the same number of doses for each of the three influenza strains would need to be produced rather than the processes operating for the same amount of time for each. Therefore, the harmonic mean is used to calculate the expected yield rather than the arithmetic mean (Ferger).

4 Results

The capacity model produced in this study was successful in utilizing an operations based methodology to calculate the vaccines manufacturing network capacity for Novartis Vaccines. The final model is able to quantitatively and visually represent both the expected utilization of the network capacity and the surplus or deficit of capacity needed to meet demand in a given year. This model was developed in conjunction with process owners from each of the Novartis Vaccines facilities and the methodology validated against the output of an operating line using its operating parameters. The model results showed good capacity agreement with the validation line with the output within five percent of expected capacity.

This model has achieved buy in with key process owners and strategic planners, due largely to the involvement of many of the process owners and operations strategy in the development and validation of the capacity model. As a result of the buy-in and transparency of this model, the long range planning model has been adopted for use in the annual strategic planning cycle.

In addition to the capacity planning results of the model, the model development and data collection cycles were useful in providing additional understanding and insight for process owners on the maximum capacity and utilization of their facilities as well as transparency in process parameters between the sites and global organizations. These efforts enabled the development of a set of Novartis Vaccines specific recommendations based on observations of best practices and lessons learned and observations of the capacity planning exercise.

4.1 Scenario Analysis

In addition to the base long range planning model, to make the model a tool that could be efficiently used in strategic planning the ability to conduct scenario analysis was added to the model. Scenario analysis operations parameters include:

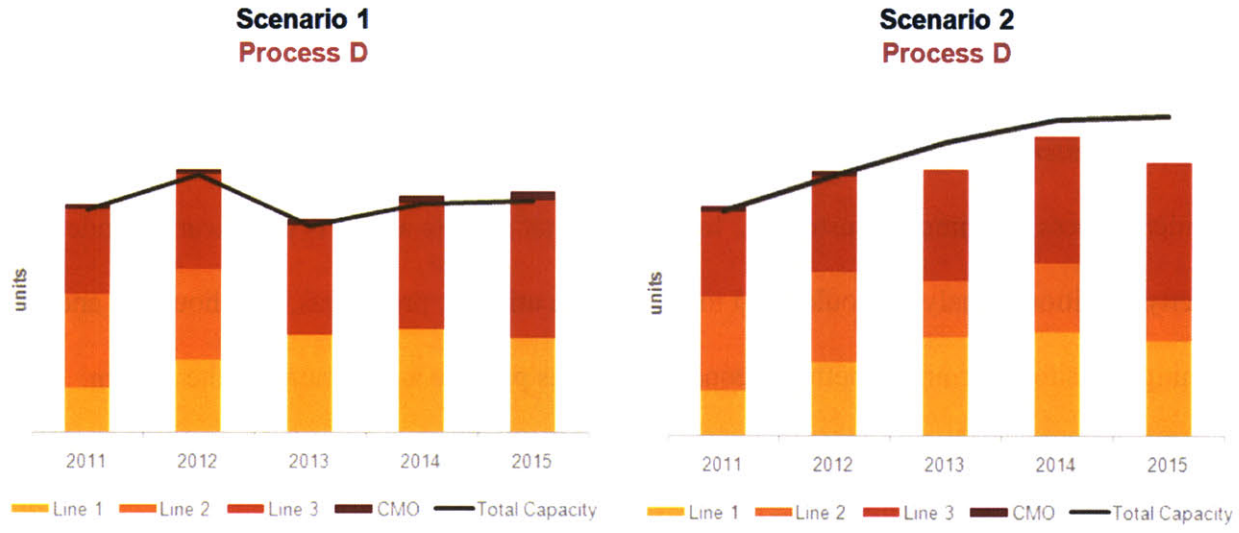
- Demand variation
- Offline capacity
- Flu yield scenarios
- Operating days per week
- Weeks of seasonal production
- Product presentation split
- Batch size
- Gap reporting units

Scenario analysis for each of these parameters is built into the model to give decision makers efficient access to the network capacity utilization results of manipulating these operational levers in different years. Scenario analysis is particularly useful when examining the effects of multiple simultaneous changes on the multi-product, multi-facility non-linear optimization.

Figure 12 illustrates an example of scenario analysis. Both scenarios are of a multi-product, multi-facility analysis for Process D. Scenario one illustrates the base case analysis, which includes a shutdown of processing line two in 2013. Scenario two examines the effects of an

upside demand scenario and the line allocation and utilization effects of a specific set of operational levers that were selected to attempt to meet the demand. In this example scenario, continued operation of line two was used in 2013 -2015 and incremental additional process improvement was assumed in 2013 and 2014.

Figure 12: Scenario Analysis[4]



4.2 Assumptions and Limitations

The Long Range Planning model makes a number of assumptions and has limitations. Both should be taken into account when utilizing the model. The key assumptions and limitations surround the timeframe of the model and variability associated with each of the parameters utilized in the model.

Maximum Operations Assumptions: The model assumes operations 24 hours a day and seven days per week, however for facilities operating significantly under that capacity there may be significant challenges and ramp up required to operate in that manner. For example, in facilities

[4] All demand and process data and analysis are illustrative only

that operate substantially under the maximum capacity the operations schedule may be optimized to minimize cost. As a result often production schedules are based on operations personnel doing the same activity at the same day and time of the week each time that it is conducted. This may create significant scheduled downtime into the system. Producing on a true 24-7 operations schedule may require greater flexibility in the workforce so that each shift being able to do a wider variety of production activities as a specific processing step would likely not always fall in the same shift on a maximum production schedule.

Secondary System Limitations: The capacities calculated in the long range planning model only consider process equipment constraints. In facilities that operate at levels significantly under capacity, additional analysis would need to be done on utilities, prep areas, warehousing, and gowning areas to determine whether secondary systems provide a constraint on the system.

Data Availability Limitation: At the time of the development of this model, some of the required data had limited availability and in some cases operations parameters were estimated based on a very limited amount of data, or on the operating experience of process owners. In many cases data availability is expected to increase as time progresses and the capacity calculation process is repeated and continuous improvement efforts collect more data. However, in some cases the data collected on operations at far below the maximum capacity may be substantially different than it would have been at maximum capacity. For example, for equipment reliability the amount of process downtime or batch delays caused by corrective maintenance and unplanned line stoppages may be far greater at maximum capacity than at a smaller utilization due to machine stress and scheduling effects.

Data Variability Assumption: Operations parameters in the model are treated as deterministic although they actually have a large degree of variability. Although using losses to approximate

the mean expected value for these parameters may be accurate on average due to the fact that the central limit theorem can be applied to many of the processes, utilizing the expected value ignores delays that would result in the schedule as a result of variability could decrease the practical operating capacity.

Demand Variability Limitation: The long range planning model currently utilizes the expected value of the demand for capacity planning purposes. However, planning capacity for the expected value of demand means there is a 50% probability that the demand will be greater than expected and the market will be shorted. In industries where it is critically important for regulatory or financial reasons not to short the market, it is beneficial for companies to plan to a higher service level to meet this demand variability. Equation 28 gives the equation to calculate the required capacity based on demand variability indicated by the standard deviation of demand and z, the service level factor that corresponds to the service level that the company seeks to provide. This optimal service level varies for each product and is based on the cost of holding too much capacity as compared to the cost of shorting the market.

$$\boldsymbol{Required\ Capacity = Average\ Demand + (z \times Standard\ Deviation\ of\ Demand)},$$

Equation 28

Model Update Limitation: Because the model is not currently linked to an external data source, it must be updated regularly on a manual basis for the output of the model to be accurate.

Non-linear Programming Limitations: The use of Non-linear Programming assumes deterministic demand, and if integer constraints are utilized this drastically increases the computational time providing a significant barrier to running multiple scenarios. Additionally, the use of this tool, which may be unfamiliar to the model operator may provide a substantial barrier to major updates of this system.

5 Conclusions and Recommendations

5.1 Business Application and Recommendations for Novartis

The fundamental premise of this project was to develop a model that facilitates identification of gaps between demand and Novartis Vaccines' ability to supply vaccine materials in the two to five year timeframe. In itself this is an important and cost saving step for Novartis Vaccines. The model also allows advance identification of time periods where current production capacity is unable to meet expected demands. This advanced identification allows strategic planners to take appropriate steps to bridge this gap in a timeline where they are useful. The timeline allows them to seek proactive cost efficient alternatives to production deficits rather than reactive alternatives that can be extremely costly or dramatically shorting the market, which could not only deprive people of life saving vaccines, but also damage Novartis' reputation.

Timely identification of these gaps allows for production validation and planning of phase III clinical trial material in facilities that have surplus capacity and appropriate processes. Being able to look ahead and plan around these gaps is important for clinical material because assuming capacity is available, internal production is generally much more cost effective than third party production for clinical trials. Additionally, generally production for the commercial launch occurs at the same production facility as produced the material for the phase III clinical trial so committing to internal versus third party production requires a confident view on what the internal production availability is for several years to come. Therefore confident identification of available capacity opportunities for internal phase III and commercial launch from existing facilities represents an opportunity for large cost savings over third party manufacturing. This is especially true since Novartis would already be bearing the fixed cost of these internal facilities.

In many organizations these opportunities go unrealized because drug development and manufacturing are often organizationally separated and undergo separate planning processes by their respective departments (Simchi-Levi, Kaminsky and Simchi-Levi 2008).

In addition to clinical trial material, production facilities regularly undergo planned capital improvement projects, which have a variety of purposes including regulatory compliance or capacity additions. With a long term view of the demand and how both the losses due to the project downtime as well as capacity additions resulting from the project impact Novartis' ability to meet demand, these projects can be scheduled at a time where the losses will have a minimal impact but the improvements from the project come online within the most useful timeframe.

Prior to this exercise, both the definition of capacity as well as capacity assessment at Novartis Vaccines was conducted in a decentralized fashion and the variety of capacity definitions, methodologies, and assumptions made it difficult to compare capacity utilization across different processes or even understand varying capacities calculated for the same process. Having a common reliable, consistent, and transparent methodology for all of the production process encourages: confidence that capacities are backed by supporting data from the operations, a common platform to assess systematic modifications and utilizations because all processes are assessed using the same methodology, and open and transparent capacity calculations discourages capacity hedging or capacity assessments that are limited by the current production schedule.

The scenario analysis capabilities of this model allow planners to quickly see the effects of changing various production levers on the process and overall capacity as compared to the demand. Additionally, it allows planners to visualize the response of the production system to a

variety of external factors such as increase or decrease in demand, and shutdown of a line or production facility. This will allow planners to "try out" different strategies to see their impacts on the production system without starting the analysis from scratch.

In addition to general capacity analysis, the long range planning model considers the effect of different product mixes on a production facility as well as providing multi-product, multi-facility decision support. The model is a dynamic tool that allows planners to quickly assess the impacts of among other things regulatory production, batch size, and product mix changes on the multi-product facilities and multi-product, multi-facility networks.

In addition to the direct planning benefits from the development of the Long Range Planning model, there are a number of secondary benefits that this global methodology provides to Novartis Vaccines, especially as Novartis carries forward using it in future model updates. When Novartis acquired the vaccines division from Chiron, each plant was operated almost autonomously. As Novartis seeks to develop its production facilities as a manufacturing network, there are a number of benefits that arise beyond planning efficiencies.

Common view of capacity versus capability: In a manufacturing organization, it is not uncommon for manufacturing personnel to be geared towards thinking in terms of how the facility is currently operated. While this may be beneficial in the present, it is harmful if it limits thinking on the possibilities of what can be produced there. Using this operations approach to calculating the realistic production potential of the facilities illustrates the differences between capacity and current capability, as well as opens the lines to thinking on how to increase capabilities.

Common language for capacity terms: In an organization where terminology is not consistent, it is difficult for efficient communications to occur and increases the probability that a mistake will be made based on the communication gap in terminology. The development of a consistent methodology for all of the facilities necessitated the definition of consistent terms for the components of this methodology. Having consistent terminology will assist not only capacity assessments, but also sharing lessons learned between facilities, technology transfers, and process improvements.

Process comparisons between facilities: The data transparency and global view of the capacity analysis gives the update team a unique view that is both high level but also delves into specific data from all the processes. Some of the data lends itself to direct comparison between different facilities and the common approach means that the team is able to make an apples to apples comparison. For example, if two different facilities were producing the same product using the same technology, but one of them had a product changeover time that was many times greater than the other, then by highlighting the differences there exists the potential for the facilities to learn from each and potentially for greater output from the facility with the longer turnover time.

Identification of key areas to target process improvement initiatives: The basic capacity methodology involves first calculating the maximum theoretical capacity and then identifying losses from this theoretical maximum. By highlighting losses in the system, it is easier to identify key areas to target process improvement initiatives, as well as key processes that really need process improvement to increase capacity to meet demand. Additionally, by using the scenario analysis tools in the model, the long range planning model can identify the expected long term capacity effect of reductions.

Proactive use of positive demand gaps: Positive demand gaps, or surplus capacity identified in the model represents opportunities for the organization. Where the gap is steady or positive and widening, this may represent opportunities for manufacturing of clinical trial material and introduction of new products. Where the gap is positive in early years and decreasing to a capacity deficit, the positive gap in early years represents the potential for capacity and resources to be utilized in capital development and/or process improvement efforts to increase the available capacity in the existing resources.

Greater data consistency: Data consistency across processes and project evaluations is important to ensure that projects and processes can be compared and analyzed on a common basis. Definitions and data accessibility for items such as: equipment capacity, maximum planned equipment utilization, lead times, and demands are standardized in the use of the long range planning model methodologies. This makes these pieces of data not only readily assessable to planners and other project evaluators, but allows everyone to makes comparisons on the same basis.

5.2 General Implications for Other Companies and Industries

Although the Long Range Planning model in this project was designed and developed specifically for Novartis Vaccines, many facilities across both the pharmaceutical industry as well as many other industries face the same difficulties of understanding how to plan for their capacity. Capacity planning is especially challenging in multi-product facilities and multi-product, multi-facility allocation decisions. For processes that follow the same operational logic and batch processing, the methodologies described in this paper for modeling and understanding these complex situations hold no matter what the product.

Many of the recommendations that apply to Novartis also apply to other companies and industries. Operations-wide understanding of capacity principles is needed to:

- facilitate planning
- help operations staff understand the impact of actions and decisions on production capacity
- generate appropriate metrics/data collection
- understand losses to drives continuous improvement

Additionally, some of the benefits of common language and common capacity-related thought processes can not only facilitate communication where the concepts or terminology apply to other situations, but also common thinking around a methodology that can be used to facilitate thinking about opportunities for continuous improvement and building a continuous improvement culture.

5.3 Areas for Further Research and Model Development

Development of this model has provided a solid first step for capacity analysis and planning at Novartis Vaccines. However, there are a variety of opportunities that exist to continue to develop this model and further refine some of its assumptions and limitations.

Capacity Monte Carlo Analysis

Currently, the Novartis Vaccines & Diagnostics Long Range Planning model assumes static average yields and process times for each process. Enhancing the planning model with Monte Carlo analysis with probability distributions for average yields and process times based on historical data would provide a better picture of the potential capacity variability.

Demand Monte Carlo Analysis

Similarly, in the current model, demand is taken as the expected value for demand in each year. Because a portion of the demand in the vaccines industry comes from all or nothing vaccines tenders with governments, company specific demand for a particular vaccine often follows a non-normal probability distribution. Understanding the probability distribution for each vaccine in the demand forecast and incorporating this into the long range planning model using Monte Carlo analysis would allow both the commercial organization and planners to understand how prepared the organization is to respond to variability in demand.

Formal Annual Update Process and Site Trainings

Because of the newness of the capacity methodology concepts and difficulty of many site data holders of being able to think of how their process would operate unconstrained by temporary capability constraints (manpower, scheduling, etc.), one on one trainings and small group trainings were part of the model development and buy-in process. However, the annual capacity model updates still require oversight from the global organization to ensure consistency of definitions such as cycle time and takt time and to push back on assumptions of capability versus capacity. Going forward, additional trainings will be needed to ensure that the staff involved at the time of each annual update understands the appropriate assumptions and data required. It would be beneficial to develop a formal annual update process for the model and site trainings on capacity so that as the capacity concepts become more widespread, that each site can take ownership of updating its own capacity model.

Integration with Process Data Databases and SAP

As the data required for the update of the capacity model becomes available in process data databases and SAP, it would be beneficial to integrate the long range planning model with these systems. Integration with these systems would allow for continuous and automatic update of data parameters as they change in the system in the databases and SAP without manual intervention. Integration with these systems would allow the planning cycles to be more resilient and responsive to changes in demand or manufacturing abilities especially if the long term planning was integrated with short term planning.

Integration with Short Term Planning

Currently the manufacturing strategies for zero to two year and two to five year manufacturing are conducted by separate organizations within Novartis. The integration of the zero to two year timeframe into the model with appropriate assumptions for that timeframe, would help Novartis Vaccines develop a consistent manufacturing strategy between the two timeframes.

5.4 Conclusions

This thesis has demonstrated a capacity calculation and analysis methodology that is based on operations principles, data, and optimization techniques. This methodology enables Novartis Vaccines to efficiently calculate and analyze capacity of their vaccine manufacturing network, but is also widely applicable to other companies and industries that utilize batch processing. Timely identification of expected production shortfalls allows planners to seek proactive cost efficient production alternatives, and production surplus identification allows for planners to identify appropriate capacity for validation and production of phase III clinical trial materials or other strategic production initiatives.

Additionally, transparent model methodology based on analysis of process losses facilitates identification of high impact process improvement areas and scenario analysis tools facilitate rapid analysis of potential process or demand changes in both single product and multi-product facilities. This enables planners to rapidly understand the network capacity utilization effects of manipulating a variety of process decision levers incorporated into the long range planning model.

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Appendix A: Variable Definitions

Variable	Name	Description
B_{Aijp}	Average Batch size	Average number of expected million doses per batch (or million dose equivalents) for product "i" on step "j" of process "p"
B_{Nip}	Number of batches	Number of batches produced annually of product "i" produced on process "p"
B_{Sijp}	Sustainable simultaneous batches	Number of batches that can sustainably occur simultaneously on step "j" of process "p" while producing product "i"
B_{Tijp}	Theoretical Batch size	Theoretical number of expected million doses per batch (or million dose equivalents) for product "i" on step "j" of process "p"
B_{Wijp}	Batches per week	Batches produced per week on step "j" of process "p" while producing product "i"
C_{ijp}	Step Capacity	Practical operational capacity of step "j" of process "p" while producing product "i"
C_{py}	Process Capacity	Practical operational capacity of process "p"
D_{iy}	Demand	Demand of product "i" in year "y"
D_W	Operating days per week	7 days
F_{Dp}	Downtime Planning factor	Percentage of available time impacted by unplanned down time such as line stoppages and corrective maintenance on process "p"
F_{Sip}	Batch success rate	Percentage of initial batches that successfully grow product within specification for product "i" on process "p"
F_{Up}	Uptime Planning factor	Percentage of available time not impacted by unplanned down time on process "p"
F_{yip}	Batch yield	Percentage yield of the initial batch size for product "i" on process "p"
H_{Apy}	Available hours per year	Hours that process "p" can operate per year after considering downtime
H_{Bip}	Batch Changeover time	Hours required to clean, sterilize, and set up for the next batch between batches for product "i" on process "p"
H_{Cip}	Product Changeover time	Hours required to clean, sterilize, and set up for the next product after product "i" on process "p"
H_D	Maximum hours per day	24 hours

H_{Tijp}	Takt Times	Hours of process time after one batch starts until the next batch begins for product "i" on step "j" in process "p"
H_{Tijp}	Batch processing time	Number of hours of active batch processing of product "i" on step "j" of process "p"
H_{Zjip}	Cycle Time	Hours that one batch of product "i" is required to occupy the process vessel(s) for step "j" in process "p"
L_{Bjp}	Batch loss	% batch loss due to lack of cell growth on step "j" of process "p"
L_{Yijp}	Process yield loss	% process yield loss for good batches on step "j" of process "p" while producing product "i"
P_{LT}	Primary lead time	Minimum time in months required from end of bulk production to final product release
R_{Sp}	Line Rate (Secondary)	Production rate in units/min on process "p"
S_{LT}	Secondary lead time	Minimum time in months required from filling to final product release
U_{jp}	Step Utilization	% utilization of step "j" of process "p"
U_{py}	Process Utilization	% utilization of process "p" in year "y"
W_{Apy}	Available weeks per year	Weeks that process "p" can operate per year after considering downtime
W_{Cpy}	Weeks of Clinical and Project production	Weeks of non-commercial production due to clinical and project production on process "p" in year "y"
W_{Dpy}	Weeks of Product Changeover	Number of weeks of productive time loss due to changeover between products for product "p" in year "y"
W_{fpy}	Weeks of Media Fill	Weeks of non-productive processing due to regulatory sterility testing on process "p" in year "y"
W_{Mpy}	Weeks of Planned Maintenance	Weeks of annual scheduled maintenance on process "p" in year "y"
W_{Rpy}	Weeks of Ramp Up after Shutdown	Weeks of time required after process start up to start out putting product again on process "p" in year "y"
W_{Spy}	Weeks of Seasonal Production	Weeks of production for seasonal influenza production on process "p" in year "y"
W_Y	Maximum weeks per year	52 weeks
T_{Upy}	Time Utilized	Total hours of time used for all functions of a production facility for process "p" in year "y"
T_{Apy}	Time Available	Total hours of time available for all functions of a production facility for process "p" in year "y"

F_S	Scaling Factor	Scaling factor applied to the number of external batches produced to minimize the number of batches allocated to external capacity during batch allocation

Subscript Definitions:

y	Year
i	Product
p	Process
j	Process step