Project Number: ZAZ-A092

Novartis Supply Chain and Diagnostics Modeling

A Major Qualifying Project Report:

submitted to the Faculty

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Degree of Bachelor of Science

by

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Abstract

The goal of this project was to analyze the Novartis Vaccine and Diagnostics supply chain. We first constructed a value stream map of Novartis swine flu vaccine supply chain based on extensive data collection and analysis of existing operational structures. We then created an Excel based simulation tool that determines the time-dependent dosage demand for the manufacturing system. Finally, we compared Novartis supply chain with the top players at strategic level to generate more suggestions for Novartis future improvement efforts.

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1. Introduction

1.1 General Overview

The swine flu, also referred to as its scientific name H1N1, erupted in the early spring months of the year 2009. These traces were discovered in southern regions of Mexico and quickly spread from pigs to the human race. From Mexico, the influenza spread north into the lower United States areas. It slowly began spreading nationwide from human to human contact and infection. It is closely compared to the seasonal flu in that the virus is contagious from germs spread into the air through coughing and sneezing. Before this outbreak of H1N1 in 2009, the last known vaccine was manufactured in 1976 to treat Swine Flu and the associated chronicle medical problems the virus caused (Google Health, 2009).

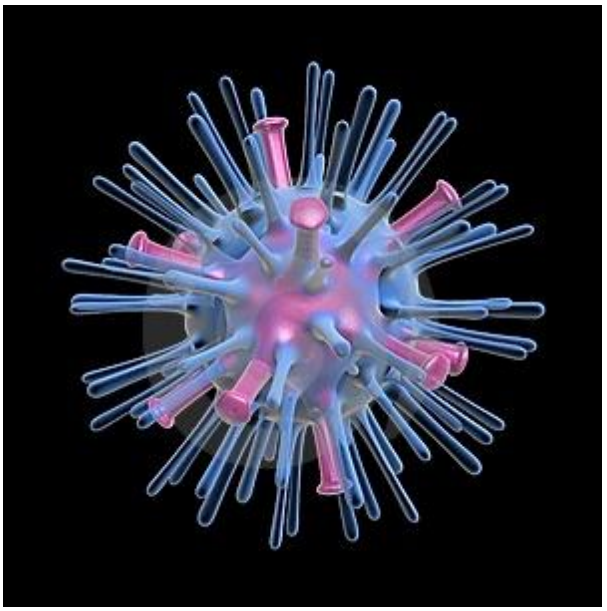

Figure 1: Microscopic Flu Virus

After a military soldier serving at Fort Dix died during a training exercise from a flu-like infection, it was determined to be the swine flu. The fear of an epidemic, similar to the plague of 1918 killing over 500,000 American citizens, erupted in the United States. It was not until President Ford took over office, who finally decided to take a proactive approach and inoculate nearly 200 million United States citizens. He proved to be successful in that the inoculation ended what was thought of as the next plague of America. This strand of flu became known as the swine flu because it was brought back by soldiers from Europe that were constantly around wild pigs and swine. This outbreak was known as "The epidemic that never was" (Mickle, 1999). Until the spring of 2009, there have been very few outbreaks and today the world is faced yet again with the challenge of swine flu and the inoculation procedures.

1.2 Company Profile

In the year 1996, two Swiss companies known as Ciba-Geigy and Sandoz combined into one major corporation called Novartis. Being a new company, Novartis set its targets out to be the world leader in it's "commitment to research and development that brings innovative new products to the community it serves" (Mickle, 1999). It accomplished this goal by providing services and products based around consumer health, genetics, and their main area of business pharmaceuticals. Novartis is a global manufacturer with locations in 140 different countries and employs nearly 100,000 people worldwide.

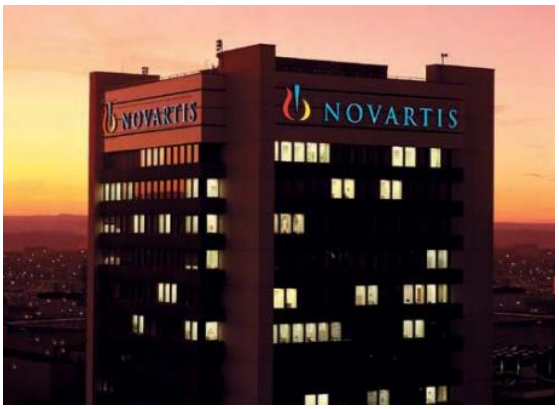

Figure 2: Novartis Vaccine and Diagnostics Headquarters

Novartis has a large network of suppliers, manufacturers, and distributors in the production and successful dispersion of the inoculants. The main source of production resides in a Good Manufacturing Practices (GMP) warehouse in Liverpool, United Kingdom that store in process material that will be filled in future batches. This is Novartis's intermediate supply for the vaccine material. A secondary production plant exists in Germany which is a slightly different from the Liverpool facility. The Germany factory manufactures products that are only formulated and then are sent to a third party supplier called Catalent. Catalent has a warehouse where the filling, inspection, and packing processes are carried out. The number of warehouses varies from country to country but there is no centralized warehouse or distribution center for Novartis to utilize.

Approximately 50-70% of Novartis's line of business is the flu vaccines and inoculations. Novartis has made the decision to not rely solely on flu products for its direct revenue and profits. As an alternative, they are investing a lot of revenue in the meningitis franchise that soon will put them strategically ahead of the competition. By bringing a never before seen product that successfully cures meningitis, will give Novartis

the competitive advantage against all contending corporations. Until the new meningitis products are launched, the flu vaccines are driving Novartis's main foundation of business and revenue.

It was not until the year 2007 that Novartis was voted on and received top notch gratification for being the number one pharmaceutical company worldwide in the industry. It relieved this rank by peer groups for the yearly Fortune Magazine issue voting on the world's most admired companies. Criteria for the first place seat included quality, service, and financial soundness. Over the past five years Novartis has risen seven ranking to stand where it is today at number one.

Figure 3: Fortune Magazine (Novartis ranked #1)

On September 3rd, 2009 Novartis finished producing an H1N1 vaccine. It was tested and in return, showed positive results and analyses in effectiveness in the immune systems response. In 80-90% of tests conducted, it enhanced the subjects' immune systems fighting off the virus. By the year 2010, the company hopes to gain permissions and approval from regulations through government agencies and begin sales and distribution around the world.

1.3 Project Goals and Objectives

After being hired by Novartis as industrial engineering consultants, there are several different tasks that we are going to accomplish. This project will initialize by illustrating a map of the supply chain that manufactures the various flu vaccine products. When the supply chain map is completed, it will be used to construct a mathematical model. This model will consist of all parameters and data taken directly from operations departments that will be able to determine the exact number of doses available at any given point in time. Being a seasonal vaccine, this is a highly complicated supply chain and presents many challenges in providing this mathematical tool package (Gardner 2009).

1.4 Project Plan

Our project plan will consist of a three pronged approach in A, B, and C terms. We will begin by doing preliminary research in A term to start the project. By the end of the term we will successfully

complete an introduction as well as a literature review that will continue to expand as our project takes off. In B term we will mainly be gathering data to map out the supply chain for the swine flu vaccine at Novartis. Once the supply chain is mapped, we will analyze the value streams to determine wastes and how we can improve system efficiency. Entering C term, we will have a broad base of recommendations that we will have analyzed data to confirm our results and reasoning's for solutions. Once recommendations are completed we will put the three terms worth of material together to form a "package" that will consist of a set of tools and maps that Novartis will be able to utilize in determining different aspects of the supply chain at any given point in time within the system.

2. Literature Review

2.1 Supply Chain Components

Supply Chain Management is used by managers to increase the overall value of their products and services for the end user; however it is also imperative to increase value for the organizations within the supply chain network. Process integration as defined in Principles of Supply Chain Management as "The means of coordinating and sharing information and resources to jointly manage a process" is the most efficient method to satisfying the goal of increased value on both ends. Examining the individual components that make up the supply chain itself provides a better understanding of supply chain integration and ways to approach improvement.

The supply chain components are separated into eight "key supply chain processes" based on the research of Lambert, Cooper, and Pagh. These processes are listed and explained in the table on the following page (Wisner 2005).

A sufficient understanding of the key components matched with strategic goals should be used to direct the integration of the supply chain process. It is critical to reevaluate the key components of the supply chain annually to identify changes involved with new products, customers, suppliers, markets and technology. Assessing the impact these changes have on the organization and supply chain as a whole will provide information that could be used to shape future decisions and help optimize the supply chain.

Table 1: The Eight Key Supply Chain Business Processes

The Eight Key Supply Chain Business Processes	
Customer Relationship Management	Identifying key customer segments, tailoring product and service agreements to meet their needs, measuring customer profitability and firm's impact on customers.
Customer Service Management	Providing information to customers such as product availability, shipping dates, order status and administering product and service agreements.
Demand Management	Balancing customer demand with the firm's output capacity; forecasting demand and coordinating with production, purchasing, and distribution.
Order Fulfilling	Meeting customer requirements by synchronizing the firm's marketing, production, and distribution plans.
Manufacturing Flow Management	Determining manufacturing process requirements to enable the right mix of flexibility and velocity to satisfy demand.
Supplier Relationship Management	Managing product and service agreements with suppliers; developing close working relationships with key suppliers.
Product Development and Commercialization	Developing new products frequently and getting them to market effectively; integrating suppliers and customers into the process to reduce time to market.
Returns Management	Managing used product disposition, product recalls, and packaging requirements and minimizing future returns.

2.2 Pharmaceutical industry overview

Every industry is plagued with problems and strife related to major changes of regulations, technology or competition. The pharmaceutical industry is no different, and the supply chain is the first thing to look at when approaching these changes. A recent study Building a Safe and Secure Pharmaceutical Supply Chain details the challenges of the modern business.

Over 40 years ago, the Food and Drug Administration (FDA) began to oversee the U.S. pharmaceutical industry in order to alleviate any manufacturing process that could endanger the lives of the end users. At that point, the industry was faced with a challenge to adapt and it resulted in high quality control from the discovery stage of a new product all the way to the dispensing process. This regulation had a positive effect on the industry giving the end user confidence to purchase safe products.

Very different challenges face the pharmaceutical industry of today. The most prevalent of these are listed below.

- Small profit margins from the failure of "miracle drugs and disappointing clinical trials.
- Protection of brand reputation with the more informed consumer searching the internet and the change to more interactive medical consultation.
- Outsourcing/off-shoring has lured American companies to lower-cost locations but the regulations of the FDA still need to be followed and new risk factors must be controlled to insure there is no reduction in quality.

Pharmaceutical companies attempt to combat these modern challenges with (primarily) three different types of supply chain strategies. The following table compares the safety and security practices across the different styles of current pharmaceutical companies (Marsh 2008).

Supply Chain Safety and Security Practices	Outsourcing-Intensive Pharma	Vertically Integrated Pharma	Contract Manufacturing
Monitoring and audit programs for direct suppliers	73%	97%	92%
Have or plan to include their raw material suppliers in a supplier qualification program	29%	67%	90%
Likely to enforce quality control and related supplier programs through SLAs	70%	81%	56%
Report doing on-site supplier facility evaluations	73%	91%	92%
Have documented and enforced process and procedures for the management of production waste, damaged, or expired product	70%	97%	92%
Have had a significant incident	91%	59%	83%
Have had a product recall	55%	47%	75%
Have or plan to introduce tamper-resistant packaging and related monitoring technology	55%	47%	75%

Table 2: Safety and Security Practices

The flu vaccine business is a subset of the pharmaceutical industry that operates within a unique niche. Influenza is a seasonal virus that is subject to frequent mutations. It is because of this that makes the industry very competitive. The six competitors are Novartis Vaccines and Diagnostics Limited, CSL Limited, GlaxoSmithKline Biologicals, ID Biomedical Corporation, Sanofi Pasteur Inc., and MedImmune Vaccines Inc.

Every season the World Health Organization (WHO) , Food and Drug Administration (FDA) and the U.S. Centers for Disease Control and Prevention (CDC) track the strains that develop in the far east as they move east around the globe. They report three strains to the manufactures to produce as a "cocktail" for the vaccine for that given season. There is a small window of time from the announcement made by the WHO, FDA and CDC until the orders need to be shipped to customers. It is in this short span that every part of the company is put to the test to be cost efficient, timely and produce a high level of quality.

Facts about influenza in the U.S. provided by the FDA
• Between 5 and 20% of the U.S population develop the flue each year. • More than 200,000 people are hospitalized. • Approximately 36,000 people die annually. • Older people, young children, and people with chronic medical conditions are at higher risk for influenza-related complications.

Table 3: Facts about influenza in the U.S. provided by the FDA

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Table 4: Supply Chain Safety and Security Practices

2.4 Process Mapping and Supply Chain Integration

Process mapping is the structural analysis of a process flow, by distinguishing how work is actually done from how it should be done, and what functions a system should perform from how the system is built to perform those functions. In this technique, main activities, information flows, interconnections, and measures are depicted as a collage on a large sheet of paper. This graphic representation allows an observer to walk through the whole process and see it in its entirety (Business Dictionary 2009). There several stages to a process map and how to initiate a sequence of events that describe the process for the product or service that is being offered to the consumer. Process maps allow the users to identify weak points in their processes. For example, in a supply chain model, the operations or diagnostics department would be able to identify any bottleneck supplies. For instance, a supplier that is constantly late on arrival times or does not deliver the requested quantities would be a bottleneck for the production lines to initiate manufacturing of the product. On the other end of the spectrum, the Distributors may be the bottleneck in the case that they are not making on time scheduled deliveries to the end user. Process maps are one of the most, if not the most useful tool in developing a strategic line of business and sound manufacturing practices from operations and production, to suppliers and distributors.

The first step of creating a process map is to specify what the product is and whether it truly is a product or if it is a service. It is much easier to create a process map for a product so it must be determined clearly whether it is a service or product. After it is determined, the process map is ready to be initiated.

There are two types of process maps that can be created. They are called macro and micro mapping. Micro maps include the smallest of steps and have very large amounts of detail for every step of the production assembly. Macro process maps include only the top levels of the process. They are extremely

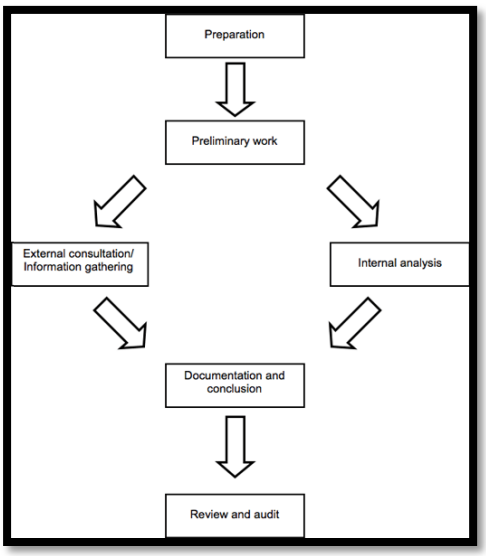

Figure 4: A graphic illustration of a simple macro process model

basic to start off an include mapping steps such as “build product”. It is crucial that the level of detail be determined ahead of time. If there is too much detail set forth, the map becomes insignificant for the main purpose. The figure to the right illustrates a simple macro process map. It has only the top level detail of production with a possible inspection step and final assembly. The elements are clearly illustrated in a way the wastes and values can be determined and analyzed for improvements. Elements that need to be tracked or analyzed become lost in the process map and sometimes never get seen when evaluating process flow.

After the level of detail has been added, such as micro or macro, the value added and waste activities can be isolated within the process map. In the process, something is value added if it makes an impact on the final assembly product. If there are steps that are unnecessary that can be taken out without failing inspection steps, it is a waste and can be removed from the overall process, which in turn reduces cycle time. However, it is value added if it is a necessary step for product performance or structure. An example of value added is that a consumer would not buy a lawnmower without wheels. The wheels are needed for performance and function of the final product so they are a value added part in the assembly process. On the other hand, a consumer does not necessarily a riding lawnmower that comes with satellite television and a microwave to make food while mowing the lawn. In this case, that would be a waste and deemed unnecessary for the final production of the lawnmower.

After the process map is completed with the desired level of detail, it can then be analyzed and evaluated for the appropriate areas of interest. Most frequently analyzed is the cycles times per station, lead times for final assembly of the product, and percent yields. To begin, the different value added and wastes can be put into a bar graph to see how efficient the system currently is running. Having high levels of waste is proven to be an unsuccessful and inefficient process. Those wastes can now be targeted and possible solutions can be initiated to eliminate the wastes and identify the value added elements of the process (Process mapping Tips 2008).

2.5 Forecast Simulation

There are several different forecasting methodologies. They are categorized as: Genius Forecasting, Trend Extrapolation, Consensus Methods, Simulation Methods, Cross-impact Matrix Method, Scenario, and Decision Trees. This project utilized simulation forecasting, in particular computer simulation to easily apply and calculate a number of mathematical analogs. Simulation forecasting allows the user to manipulate different factors and conditions in order to calculate future conditions.

2.6 Significance of Forecast Simulation

There are a few reasons why forecasting can be important and advantageous to the user. First, it enables management to modify operations at a particular time to achieve favorable conditions and benefit from the results. In addition to gaining benefits, simulation forecasting also prevents loss and destructive practices by avoiding unfavorable projected results. Essentially it presents a statistically calculated risk factor. A forecasting tool that is accurate has the ability to see what interventions are necessary to manipulate current practices to meet the business's target objectives. It is important to note that if the initial assumptions are incorrect then the forecast will reflect and amplify the errors.

Figure 5: Risk prevention through forecast simulation

2.7 Effective Conference Calls

One of the biggest obstacles our team must overcome in order to produce an effective report is dislocation. Seeing as the Novartis manufacturing plant our project is focused on is located in Liverpool, England, we must utilize certain tools in order to develop and maintain an efficient flow of information. Similar to many international professionals, we will rely heavily on the use of conference calls. Conference calls are essentially meetings conducted over the telephone used to exchange information between two or more parties. Like all meetings, there is certain criterion that maximizes the effectiveness of conference calls.

First, effective conference calls begin with preparation. If participating parties are not prepared then maximum effectiveness will not be achieved. To begin with, it is critical to schedule conference calls at convenient times for all parties involved. Additionally, it is important to prepare an environment conducive of an effective conference call. Therefore, a quiet room and necessary equipment must be reserved in advance of the scheduled meeting. Also, it is vital that all parties are prepared for what the conference call will entail. Parties should develop and exchange agendas of what their respective objectives of the conference call. This ensures that parties are adequately prepared, which results in achieving desired results. Preparation allows participating parties to efficiently utilize time and resources, which contributes to the overall effectiveness of conference calls.

Furthermore, another pivotal aspect of conference calling is professionalism. As in any business setting it is important to maintain a professional environment advantageous of achieving desired goals. It is important to keep in mind that conference calls reflect on you, you're party, and your organization. Although conference calls generally do not include visual presentation, it is critical to treat them as if they were face-to-face meetings maintaining

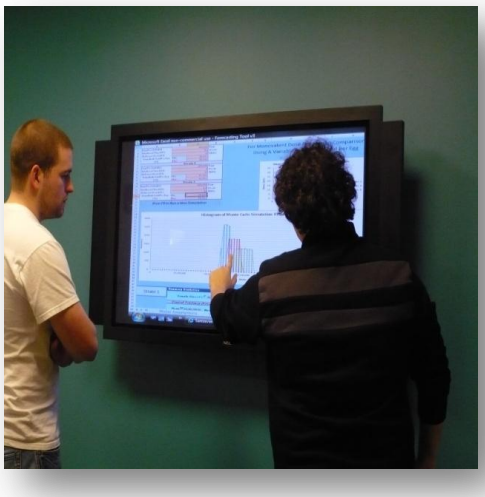

Figure 6: Our team examining strain histograms

courtesy and professionalism. A Professional environment keeps participating parties focused on the agenda and maximizes the exchange of information, which sanctions an effective conference call.

Another integral aspect of conducting an effective conference call is actions of participating parties. Prior to the meeting there is an agenda set forth in which parties must maintain focus on. The function of a conference call is to exchange information necessary for completing objectives and this must remain the sole purpose. That is why it is important not to multitask during conference calls and focus all efforts towards completing the tasks at hand. Therefore, any distractions such as cell phones, pagers, PDA's, and laptops should be turned off unless needed for the meeting. However, it is beneficial to take notes, or record, conference calls to refer back to them and ensure that no information is lost. Lastly, at the end of conference calls it is helpful to briefly recap all topics discussed and provide corresponding parties with contact information in case of possible follow up questions, concerns, or possible future topics.

Figure 7: Our team in a conference call with Novartis

Practicing the previously discussed topics will result in conducting an effective conference call. Seeing as we are relying heavily on the use of conference calling to obtain information necessary for the completion of our project, it is imperative that we utilize this tool effectively. Conference calls benefit all parties and provide participants with critical information needed to achieve established objectives. In conclusion, conference calls are a significant instrument used in the professional world and it is pivotal to maximize the effectiveness of this tool.

3. Methodology

The complexity of this project required a plan that would allow the team to efficiently address each aspect of the project. The first hurdle was to find a solution to working with a global company without being able to have regular face to face meetings with our sponsor or other contacts from Novartis. We recognized communication to be critical to the project's success and immediately sought out the resources required to set up teleconferences. Once we agreed on a weekly meeting time that worked for both our student schedules and the time difference schedule of our contacts we arranged for a room and conference phone.

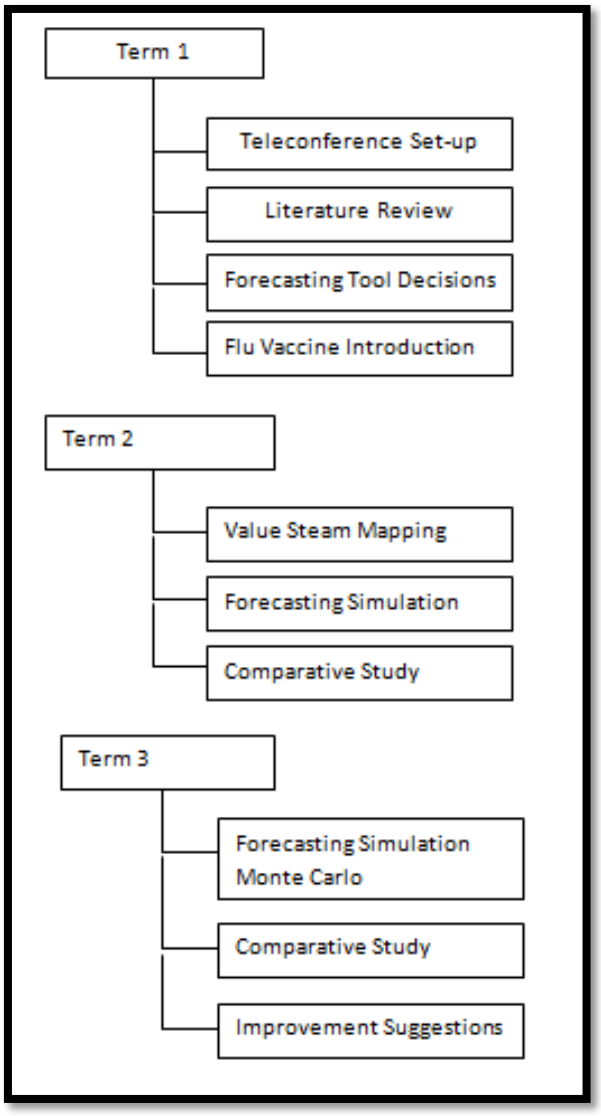

Figure 8: Term-by-term project plan

Our first term was composed of reviewing material we covered from previous studies and classes, investigating and expanding that prior knowledge, getting an introduction to the pharmaceutical industry and a crash course on the science behind the Flu Vaccine. Our examination started with supply chain components and process mapping. We applied and compared those concepts to the pharmaceutical industry as we researched the overall vaccine industry. The most difficult aspect of this term was comprehending the science behind making the flu vaccine especially since that was outside our major areas of study. We ended the term by making decisions on the forecasting tool, including the software decision, and key functions. It was decided that the tool would be an excel based tool that would utilize simulation forecasting to achieve the analysis Novartis required.

Term 2 started with an end to end value stream map. This process allowed us to not only provide the company with a great visual tool for decision making but also improved our understanding of the company and the interactions that need to be portrayed in the forecasting tool. Simultaneously to the construction of the value stream map in Visual Basic, our forecasting simulation tool was starting to take shape with the translation of processes to algorithms. This was a critical stage in communication that required two teleconferences per week to confirm the accuracy of every function and interface. This term ended with a beginning look into a comparative analysis of Novartis's practices and the industry standards.

In term 3 we continued the development of the simulation tool maintaining close communication with the Novartis contacts and expanded the program to include Monte Carlo simulations as a risk analysis function. The excel tool was also polished, refined and tested. At the same time as the software development, we also continued the comparative analysis and rounded out the term with suggestions for future practices and projects.

4. Preliminary Studies

Novartis needs to view their supply chain from one end to the other on a large scale. This would help make predictions and produce more efficiently. Not only will this increase profits, allow the company to be more competitive, but it will also provide more vaccines to people who are in need of them especially with the high demand for the H1N1 product. Below is a summary of the written and verbal details of the existing Novartis supply chain as described by David Gardner in a paper he wrote in 2008 as well as conference calls made in October of 2009.

Supply Chain Map

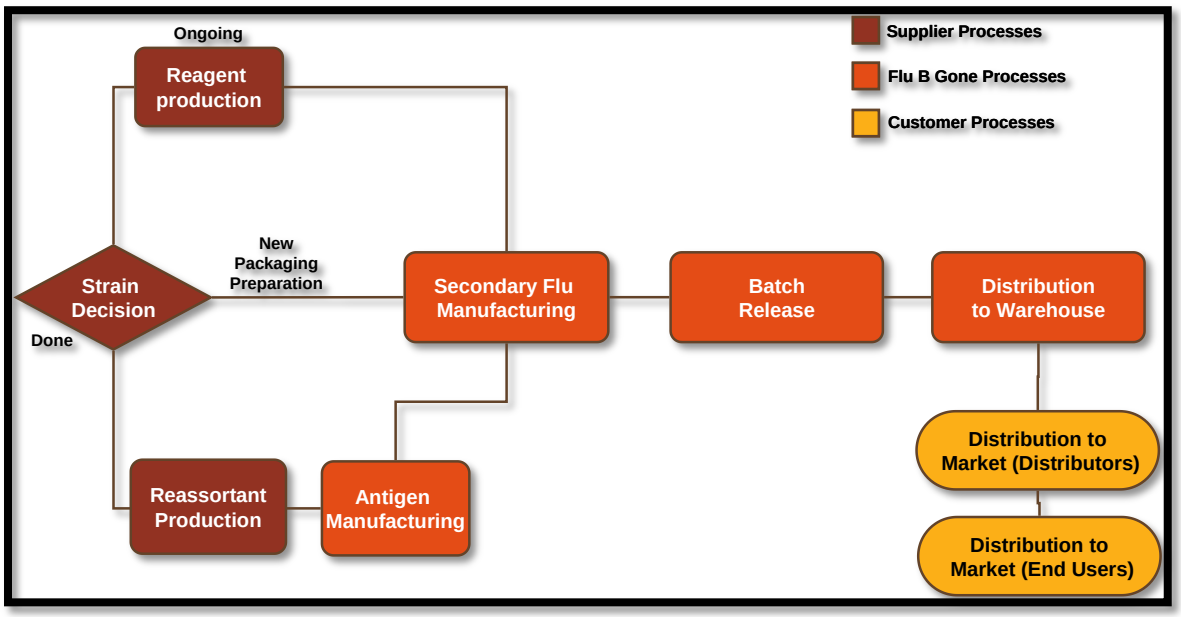

Figure 9: Supply Chain Map

The Novartis flu vaccine supply chain consists of raw materials, information and regulations. The materials are of high quality and come from various global locations. The information and regulations are provided by large organizations like the FDA, WHO and CDC as well as smaller healthcare agencies. The current manufacturing process takes place in three sites in Europe. After the vaccine is produced, it has to go through a formal quality release process which is very important for a product that is injected into the

body; however it is also an area of concern for Novartis because of its lengthy lead time. After the release process is completed, the products are shipped to warehouses around the world. From the warehouse, the vaccine is sold to distributers and later, end users. Traditionally the end user is a hospital, clinic or doctors office that administers the vaccine to a customer, but with the H1N1 pandemic, governments from various countries are also making purchases.

4.1 The Manufacturing Process

"The most important part of the manufacturing process is the production of antigen. The Flu virus has structures on its exterior that are known as surface antigens. These structures are what trigger an immune response to the virus in a human. The whole premise of the Flu vaccine is that inactivated antigen injected into the body will generate the same immune response as a person who has become ill with the virus." (Gardner, 2008)

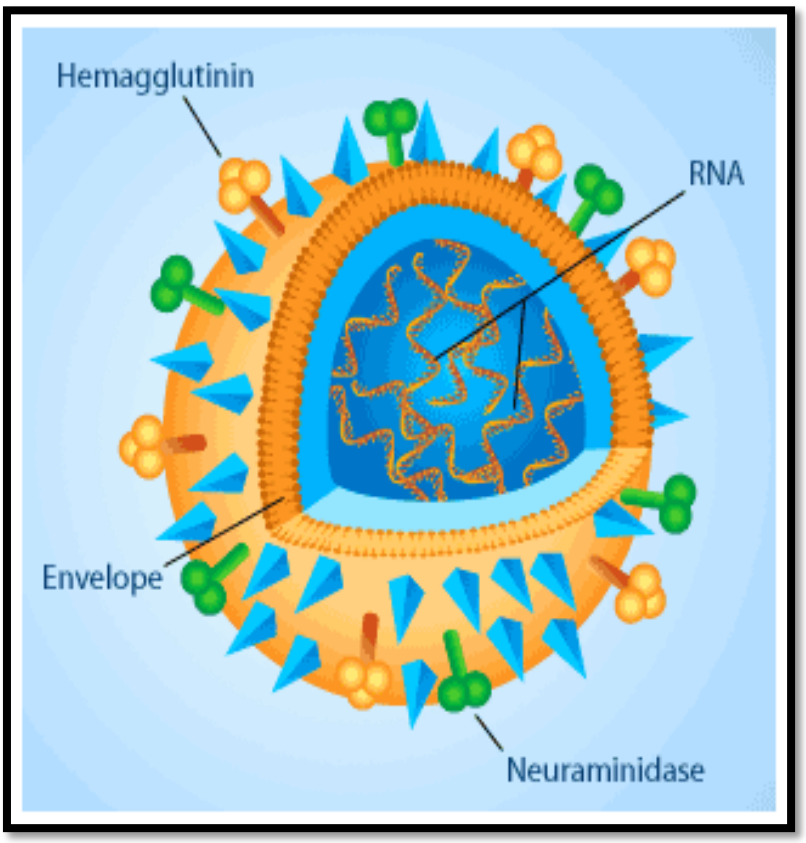

Figure 10: Surface Antigens

The manufacturing process can be broken down into several steps outlined below.

1. **Seed Development & Strain Decision**
    - World Health Organization selects strains each year (Mid February)
    - Third party institutes are continuously working on development of enhanced versions of each known strain
    - Original strain performance is compared with enhanced strain performance and selects best yielding alternatives
2. **Reagent Acquisition**
    - Reagents are needed to determine potency of manufactured product
    - Final product cannot be finished until reagents are available from suppliers (late May/early June)
3. **Antigen Production**
    - Manufacturing and inactivation of viral components that trigger immune response
4. **Secondary Manufacturing**
    - Blending of three different strains into final formulation, filling into vials or syringes, and packaging
5. **Batch Release**
    - Final quality control testing
    - Production batch records are completed and reviewed
    - Laboratory owned by the country the vaccine will be sold to, tests and signs off on the product.

Figure 11: Novartis Fluvirin Vaccine

6. **Distribution Channels**
    - After completion, the vaccines are shipped to a corresponding warehouse where they are stored until needed.

- After the need for the vaccine diminishes (September 1st) the remaining products are scrapped, reinforcing the importance of releasing as many doses as possible prior to the target date.

4.2 Forecasting Techniques

Forecasting is a process of making predictions about an unknown situation. The process itself can be separated into two types of methods: Quantitative and Qualitative. Furthermore, forecasting techniques span a wide variety of methods and applications. Novartis requires a Quantitative forecasting tool that will encompass simulation techniques. The goal of a simulation based tool is to use mathematical equations and assumptions to predict the real effects of alternate conditions and options. This allows the user to make more informed decisions and calculate possible benefits or shortcomings of any given change in scenario. The benefits of this would include increased production and identification as well as impact of major bottlenecks to name a few.

4.3 Limitations

All forecasting techniques are not without their problems. The measure of accuracy should be considered when basing a decision off of simulation based forecasting especially since simulation techniques loose accuracy the further it predicts the future. The flu vaccine is seasonal and independent from year to year with the exception of a historical based prediction of strain yields. This makes simulation ideal for forecasting dose production as well as lead times.

4.4 Software Decision

Novartis decided on using an Excel based program to host the forecasting tool. This decision was made for the purpose of both ease of use for the user and cost for the company. Alternate software is available however for

Figure 12: Excel based software programming

this particular application Novartis does not require the depth and extra features offered in other software packages.

4.5 Development

The first step in developing the forecasting tool is to understand the process that will be forecasted. This was accomplished through the end-to-end mapping of flu vaccine production. The next step was to understand what Novartis wanted. This is a common problem faced by many software developers. Customers don't always know right away what they want and the best way to approach this problem is to create prototypes and early renditions to gather feedback and gauge what is important to the end user. Ultimately Novartis is most interested in the calculation of doses produced week by week and the relationship between strain yields and lead times. Being able to predict the impact of strain yields on lead times will greatly improve decision making for production. There are secondary variables that are included in the forecasting model. These include loss at each stage, secondary manufacturing in-house versus outsourcing, quality control lead times, and the impact of adding or reducing shifts. The last variable of amount of shifts is particularly interesting considering the new data being collected on how the demand from an epidemic season should be approached opposed to a regular season.

4.6 Components

The forecasting tool consists of four major sections; Monovalent strain production, Trivalent production, Secondary Manufacturing and Batch Release.

- **Monovalent strain production:** consists of three strains and is highly dependent on strain yields taken from historical data.
- **Trivalent production:** This is a cocktail mix of the three monovalent strains and is based on the production levels of monovalent strains and rate of manufacturing (mixing).
- **Secondary Manufacturing:** This is broken into Vial and Syringe filling and packing. Major quality control steps are involved and are highly dependent on the acquisition of antigen. Also there is a

required amount of loss during this stage so that a minimum dose amount is provided to the patient. Outsourcing in another option in this section.

- **Batch Release Times:** This is highly dependent on the country and customer and may take several weeks to resolve any deviations in quality.

4.7 Statistical Simulations

Novartis is interested in a Monte Carlo analysis. The Monte Carlo method is the use of computational algorithms that utilize repeated random sampling to compute results. This is particularly fitting for this application because of the significant uncertainty in some of the input assumptions. The Monte Carlo method is also widely used to successfully investigate risk analysis. The particular approach followed by this method includes the following:

- Define a domain of possible inputs
- Generate inputs randomly from the domain using a certain specified probability distribution.
- Perform a deterministic computation using inputs.
- Aggregate the results of the individual computations into the final result.

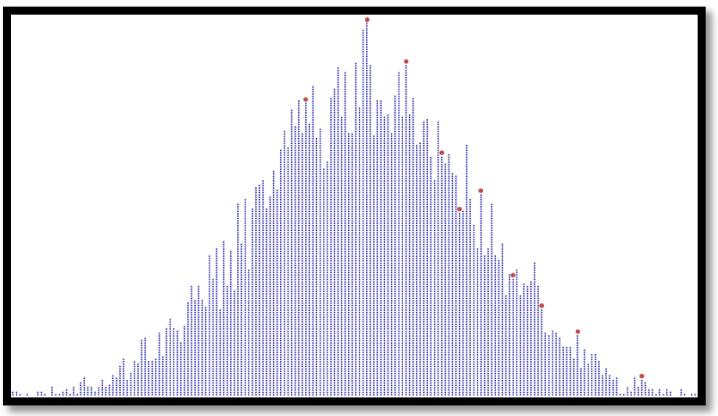

Figure 13: Normal probability distribution in Monte Carlo simulation

5. Supply Chain Analysis

5.1 Novartis Suppliers

Novartis has a very large pool of suppliers that they are able to utilize. These suppliers range from Germany, India, and even The United States. It is within these bounds that they are so successful in creating a product on time and in top notch quality. Their ability to do produce quantity as well as quality stems from the fact that they buy multiple parts and supplies from multiple suppliers. If one supplier fails to deliver they always have backups in order to fulfill specific loads and time frames through production outputs.

5.2 The Top Supply Chain

The supply chain for Novartis Vaccines and Diagnostics is a lengthy process that starts with gaining suppliers, to strategically distributing its finished products and services. The first process is primary manufacturing. It consists of first acquiring the eggs. The eggs are then incubated and the tops of the egg shells are removed. They then enter a centrifugal process and are ready to be injected. The next step of the primary process is injecting the eggs with the virus strand and removing the antigen "spikes" from the egg yolks. The antigens are removed and used in secondary manufacturing. In secondary manufacturing the vaccines are at final assembly where they are placed into syringes and vials. They are finally sent to packaging where they are placed in boxed carton containers. The carton containers are then shipped off to a warehouse where a distribution centers delivers the inoculations to the various end user locations.

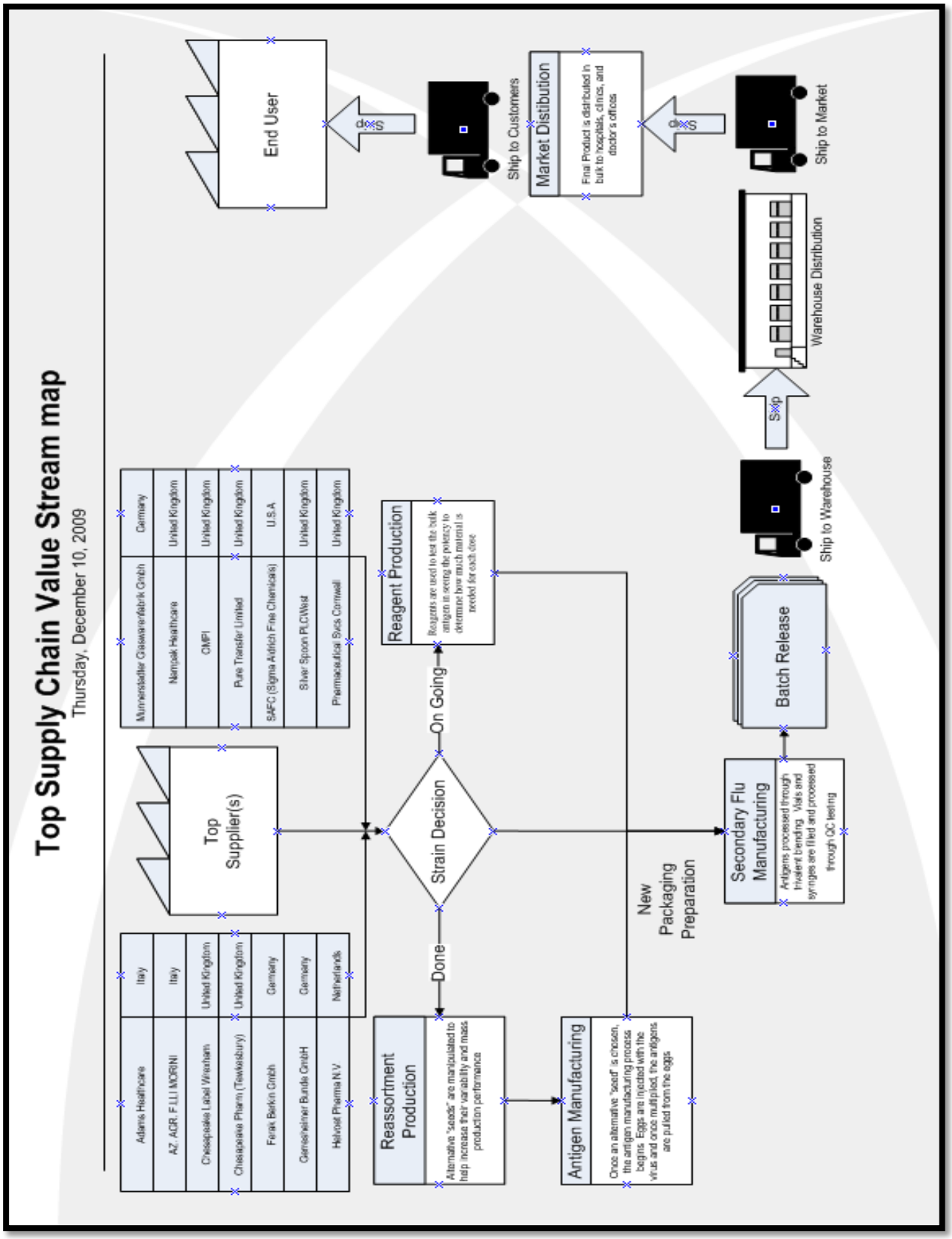

Figure 14: Top Supply Chain Value Stream map

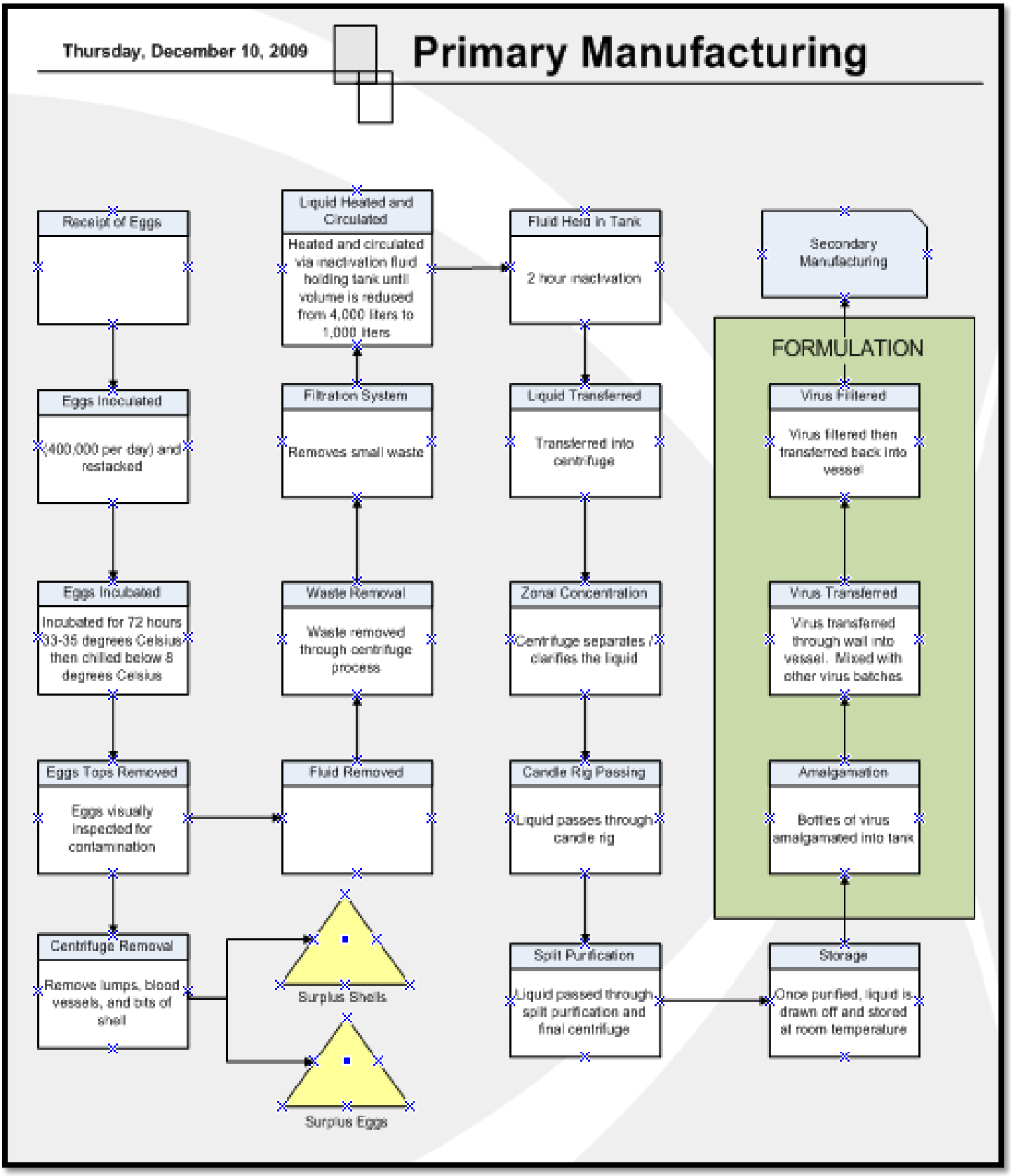

Figure 15: Primary Manufacturing

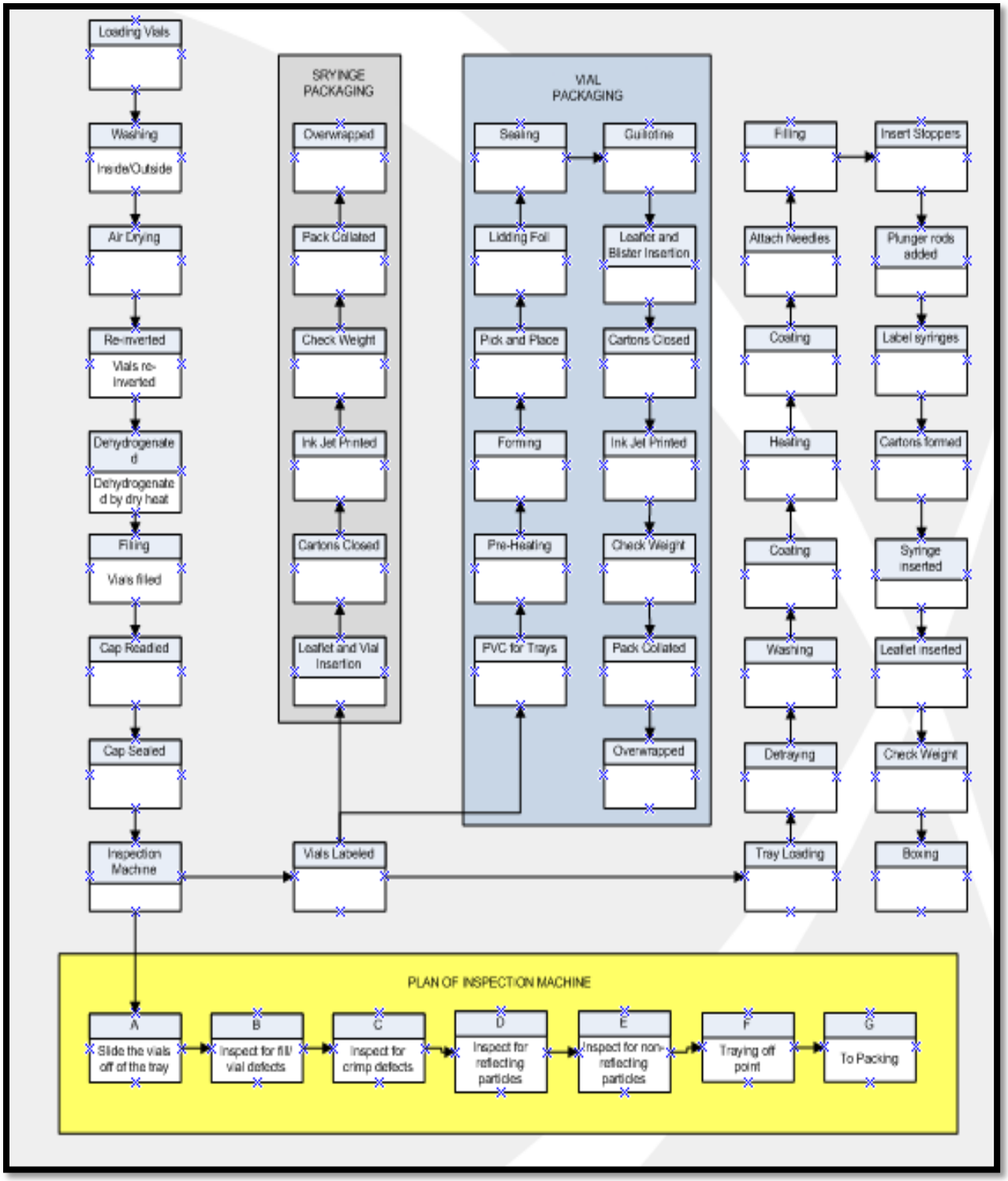

Figure 16: Secondary Manufacturing

5.3 Distribution and Transportation

Figure 17: Concept illustrating 3PL principles

Novartis utilizes 3PL concepts when relaying its products and services to several regions of the world. As stated before, Novartis has several locations for manufacturing processes. From Germany and London, all the way crossing oceans to the United States, it takes careful planning and transportation logistics to successfully complete deliveries. For secondary manufacturing, the vials are packaged and then shipped by road followed by ferry to Belgium. After Belgium, they are then shipped by air freight to Dulles International Airport. From Dulles, they are then finally shipped by road to a warehouse and distributed onward from there throughout the United States. Local distribution networks move the material from site to site across the country and distribute to the end user hospitals, clinics, and doctor's offices.

Value Stream Map

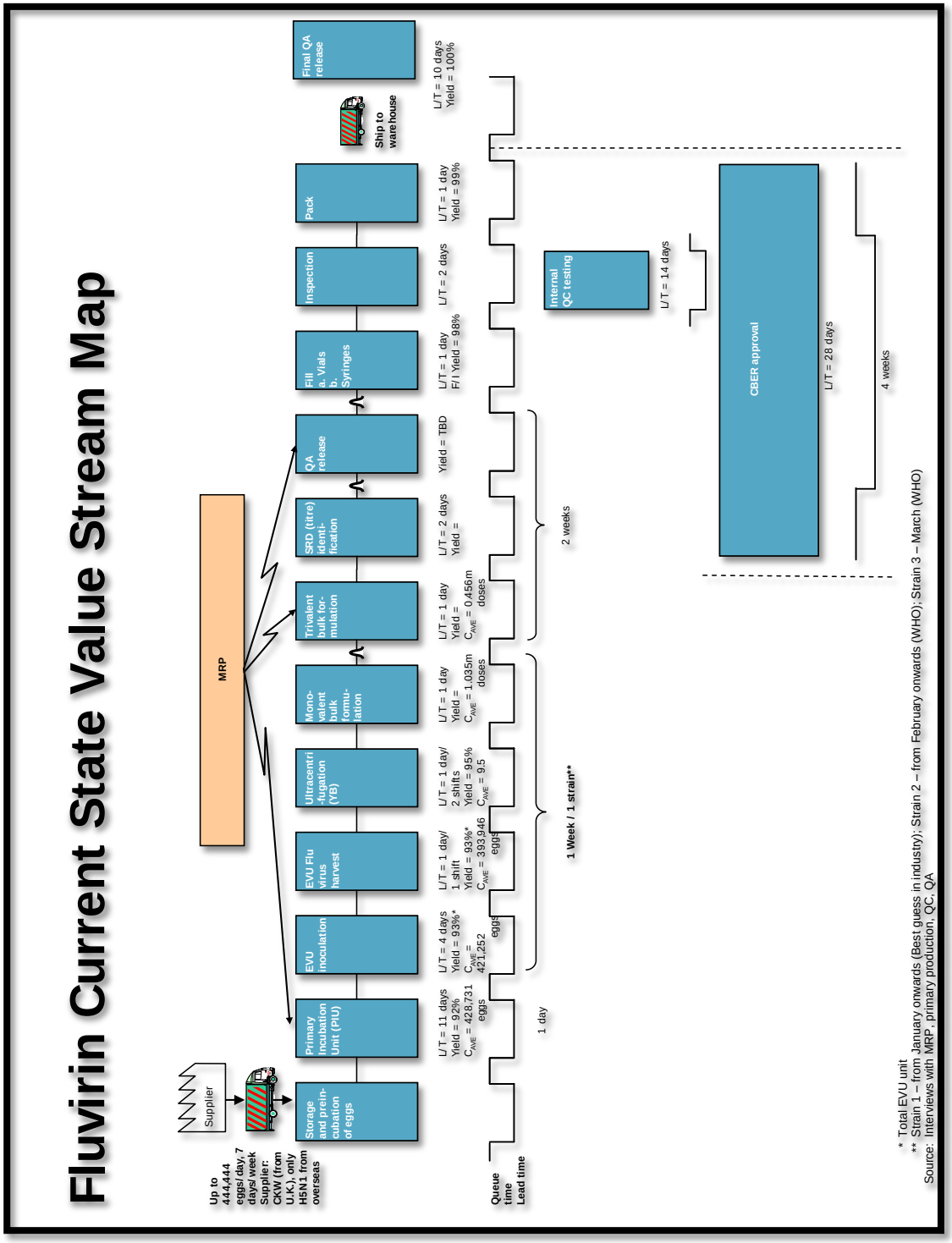

Figure 18: Fluverine Current Value Stream map

Batch Release Process

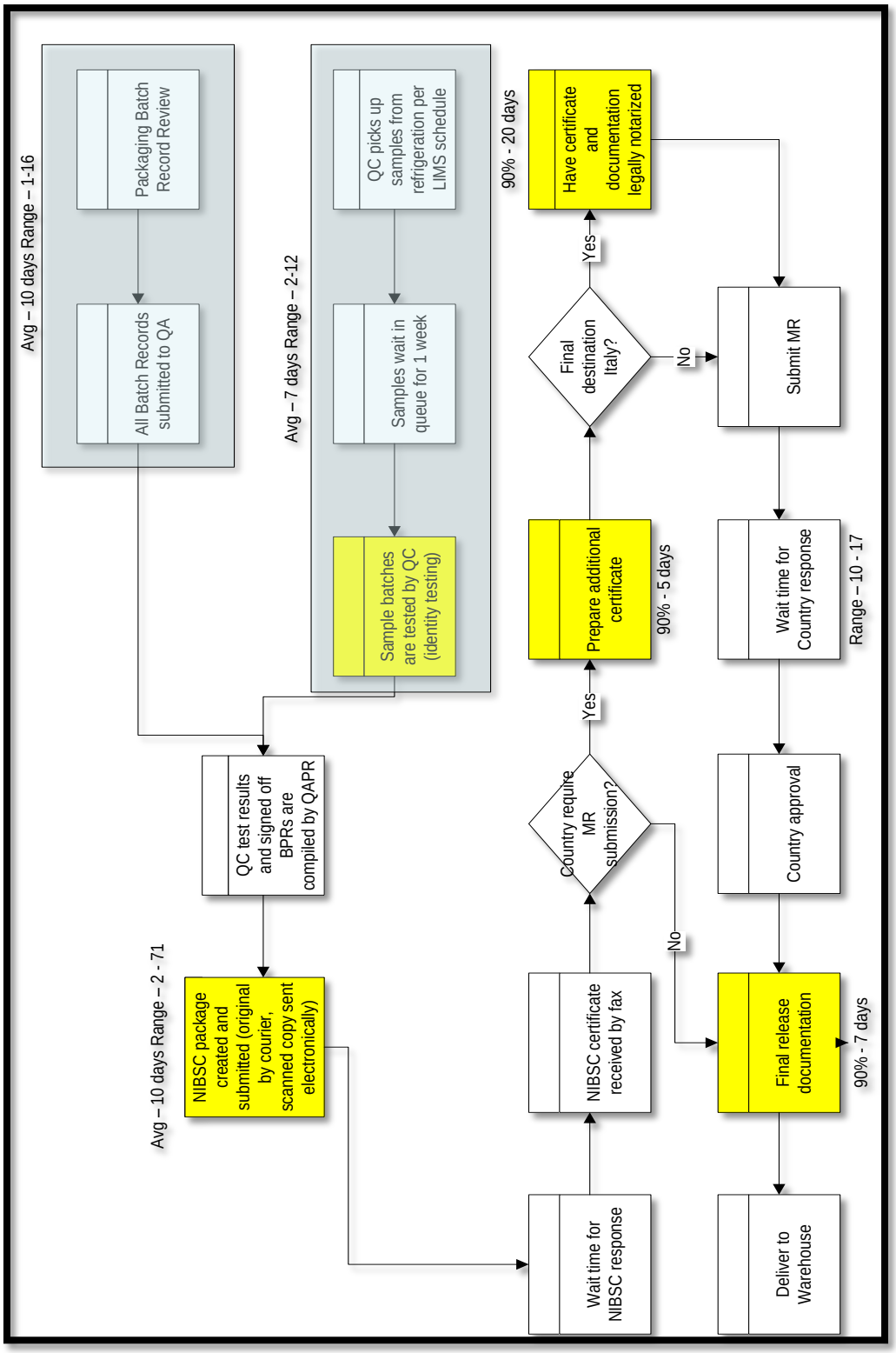

Figure 19: Batch Release Process

6. Forecasting, Simulation, and Results

6.1 Application

The Forecasting Tool created for this project has been developed for the use of Novartis Vaccine and Diagnostics to help improve decision making pertaining to Flu Vaccine Production. The goal of this model is to provide a user friendly and accurate forecasting simulation tool that will calculate and analyze both production lead time and dose amounts based on production variables. In addition to forecasting a production schedule, Monte Carlo simulations are use to help predict production values while considering the uncertainly of strain yields.

6.2 Model Platform

Numerous computer software programs exist with the sole purpose of forecasting and simulation analysis. In general, computer simulations enable thousands of mathematical calculations to run simultaneously and provide near instantaneous results. Microsoft Excel is a common office application that is easy to use and learn. Excel provided a prime platform for this forecasting tool not only because of the simple user interface but because it also provided a very flexible array of functions that encompassed all aspects of this project with no additional cost to the company. Notable software that could be purchased and used for future applications include: Crystal Ball, Risk Solver and @Risk.

6.3 Construction

An in-depth comprehension of the flu vaccine production and supply chain decisions where necessary in the development of the forecasting model. The creation of an end to end supply chain map was invaluable in understanding the complexity and numerous variables affecting the production process.

Another obstacle that was addressed in the early stages of development was the exact purpose and use for the model. It is not uncommon for clients to have a very vague idea as to what the end result of the

product should accomplish. This obstacle was overcome by following the System Development Life Cycle (SDLC) used by Management Information System software programmers and designers.

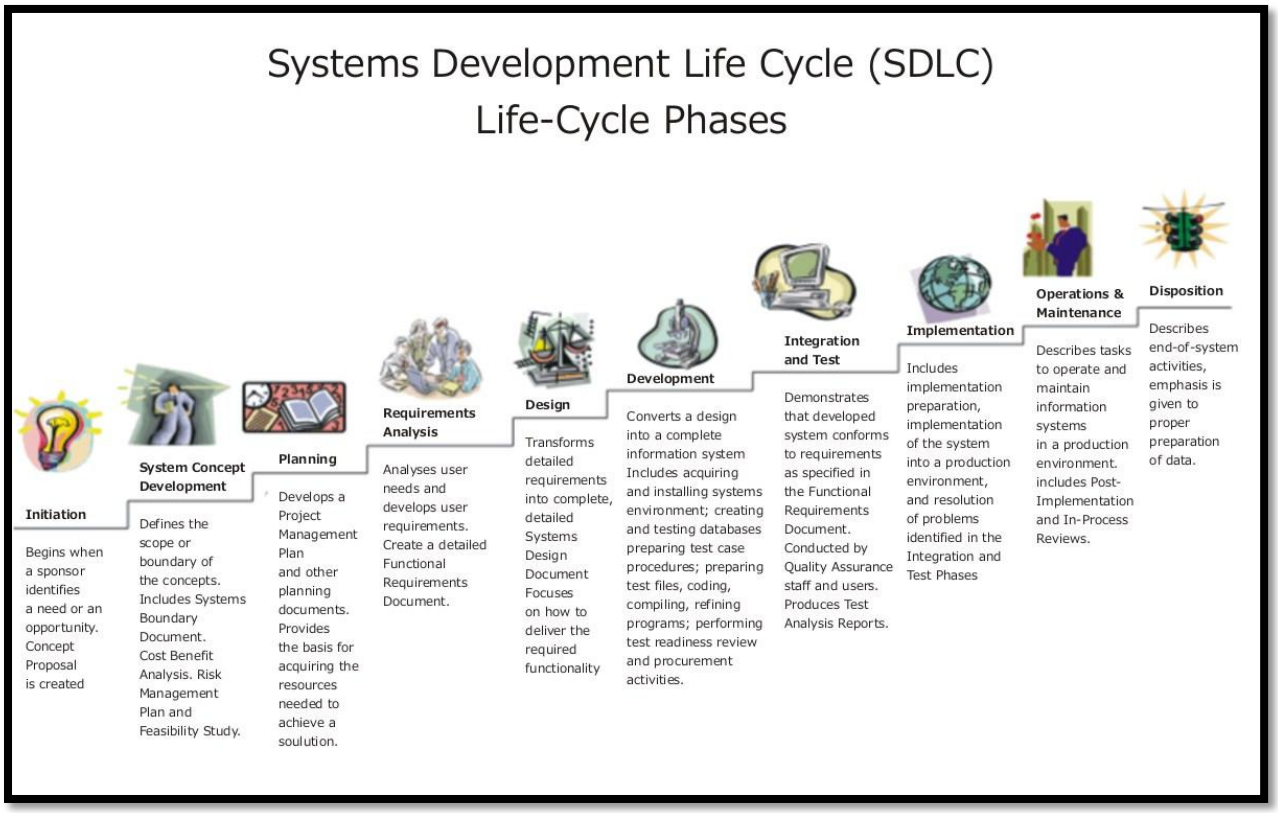

Table 5: Systems Development Life Cycle (SDLC)

Each phase (up through the Integration and Testing phase) was addressed by posing relevant questions to the Novartis contacts and systematically acquiring the information and data required to move from one phase to another. This allowed the team to more accurately address the core need and narrow down the scope from a broad and vague concept to a narrow and practical model.

6.4 In-depth Construction of the Excel Model

Below are the main components and contents of the sections in the Forecasting tool. Following that is a closer look at the input variables and the output results for each section.

Main Components	1. Lead Time Calculation
	2. Dose Production
	3. Monte Carlo Analysis
Contents	1. Monovalent Antigen Production a. Strain Yields
	2. Trivalent Blending
	3. Secondary Manufacturing a. Syringe b. Vial
	4. Production Schedule
	5. Monte Carlo Simulation a. Single Monovalent Strain Prodcution Forecast b. Three Monovalent Strain Production Forecast and Comparison

Table 6: Forecasting Tool Components and Contents

Monovalent Antigen Production:

This section covers the production of each of the three monovalent strains. Inputs and outputs are identical for each strain.

	Monovalent Antigen Production	Strain 1	Strain 2	Strain 3
3	Start Date (week number)	1	5.00	10.00
4	Existing doses	0	0	0
5	Yield (Doses/Egg, net of Overfills/Overages)	25.00%	90.00%	75.00%
6	Eggs per Shift	400,000	400,000	400,000
7	Total Manufacturing Shifts	105	105	105
8	Quality Control Lead Time (shifts)	0	0	0
9	Shifts Per Week	21	21	21
10	Total Doses	10,500,000	37,800,000	31,500,000
11	Lead Time Per Strain (weeks)	5.00	5.00	5.00
12	Total Lead Time (weeks)	15.00		

Table 7: Monovalent Antigen Production Excel Spreadsheet

Inputs:

Existing Doses: This is the number of doses already produced and could be used for an analysis part way through the production season if conditions change, or if existing inventory existed for any particular strain to lessen the need of production time on a single strain and allow for greater time spend on the other two.

Eggs Per Shift: One of the main components needed to produce the vaccine. This input won't change often however it can prove to be useful if supply fluctuates as a result of increased production.

Quality Control Lead Time: This number reflects the number of shifts in addition to regular production time that is added to lead time. Quality control is crucial in this field and the documentation or investigation into deviations can delay production.

Shifts Per Week: The amount of shifts per week can easily change depending on demand. Scenarios ran with increased shifts as a result to an epidemic year can be compared to a regular year. It can also be used to forecast the difference in adding or subtracting the shifts required to save time and money or increase production.

Lead Time Per Strain: This is the amount of time Novartis wants to produce the strain. There are many variables that go into deciding which strain to run and how early to start production but that is highly reliant on the World Health Organization. The lead time can be adjusted to achieve the desired dose amounts.

Output:

Total Doses: This is calculated by the following:

(Existing Doses + (Yield x Eggs per shift x Total Manufacturing Shifts))

Note: Yield is calculated in a subsection of Monovalent Antigen Production (following section)

Total Lead Time: This is a simple addition of all three strain lead times since each is run individually while also adding the extra quality control lead time.

A graph is included to show the difference in Strain production. Ideally they should all be as high as possible but should also be as close to each other as possible to prevent waste.

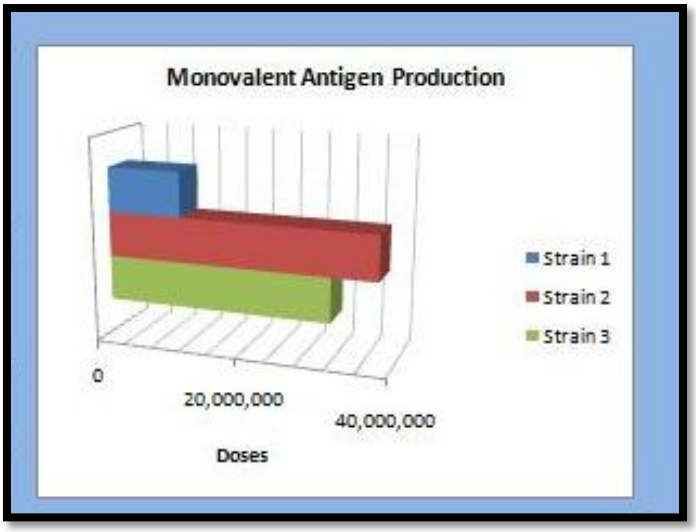

Figure 20: Monovalent Antigen Production Strains

Strain Yields:

Inputs:

3			
4	**Strain 1**		
5	Total Egg Supply	400,000	eggs/shift
6	Gross Bulk Yield Per Egg	25.00%	Dose per egg
7	Loss	75.00%	% lost
8	Net Bulk Yield Per Egg	0.250	dose/egg
9	Total Bulk Output	100,000	dose/shift finished
10			
11	**Strain 2**		
12	Total Egg Supply	400,000	eggs/shift
13	Gross Bulk Yield Per Egg	90.00%	Dose per egg
14	Loss	10.00%	% lost
15	Net Bulk Yield Per Egg	0.900	dose/egg
16	Total Bulk Output	360,000	dose/shift finished
17			
18	**Strain 3**		
19	Total Egg Supply	400,000	eggs/shift
20	Gross Bulk Yield Per Egg	75.00%	Dose per egg
21	Loss	25.00%	% lost
22	Net Bulk Yield Per Egg	0.750	dose/egg
23	Total Bulk Output	300,000	dose/shift finished
24			

Table 8: Strain Yield Calculation

Egg supply: Linked from Monovalent strain production.

Gross Bulk Yield Per Egg: This is one of the most interesting numbers in the model. Its uncertainty from year to year can only be predicted with only a limited level of accuracy since the strain yields are not only different depending on the type of strain (which changes every year) but also because that particular year the yield may be different from the past. The only way of predicting it is with historical data or after the start of production. The Monte Carlo Analysis later addresses the uncertainty of the strain yields.

Output:

Total Bulk Output: This is the amount of antigen produced per shift.

A graph to visualize the difference of shift production as well as loss per strain is available to compare any major variations that need to be compensated for in the monovalent production section.

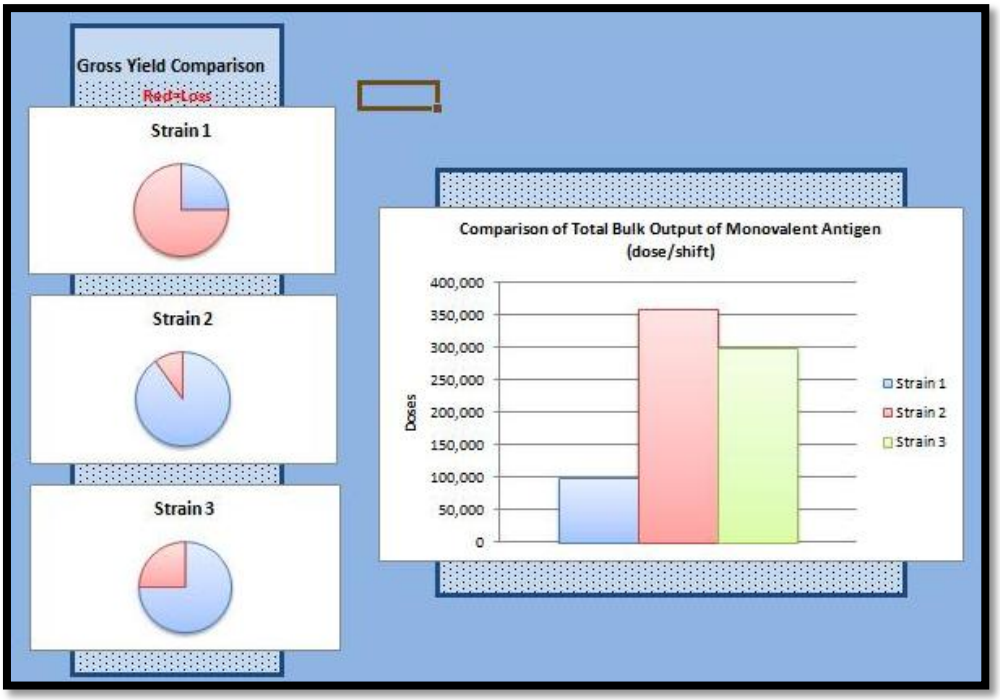

Figure 21: Gross Yield Strain Comparison

Trivalent Blend:

This section covers the blending process of the three strains into the one vaccine.

14	**Trivalent Blend**					
15	Start Date	16	Week number			
16	Possible Doses	10,500,000				
17	Rate of manufacturing	250,000	Dose/Shift			
18	Manufactring Shifts Required	42.0	Shifts			
19	Loss	0.40%	%			
20	Quality Control Lead Time	0.0	Shifts			
21	Shifts Per Week	21.0				
22	Total Doses	10,458,000				
23	Total Lead Time	2.00	Weeks			
24						
25	Excess (Doses of Monovalent per Strain)	Strain 1		Strain 2		Strain 3
26		0		27,300,000		21,000,000

Table 9: Trivalent Blending Input(s) Excel Spreadsheet

Inputs:

Start Date: This is used for scheduling purposes.

Rate of manufacturing: This is the amount of doses produces per shift.

Loss: There is a certain amount of loss during the blending process.

Quality Control Lead Time: This is similar to the Monovalent Strain Quality Control Lead Time. It should only be inputted if it adds to the overall lead time.

Shifts Per Week: The amount of shifts per week the blending process is run. This may change depending on demand.

Outputs:

Total Doses: The total amount of doses produced after the loss from the blending process.

Total Lead Time: Amount of time the process takes.

Secondary Manufacturing:

This covers the finish, filling and packing (FFP) of both vials and syringes. The Liverpool site does not have a syringe line so it is outsourced to another site. Since the inputs and outputs are nearly identical they will be cover together.

31			
32	Doses for Vials	725,000	Doses
33	Start Date (Vials)	20	Week Number
34	Vial Fill Loss	2.00%	%
35	Doses per Vial	10	Doses/Vial
36	Vial Fill/pack rate	72,000	Vials/Shift
37	Quality Control Lead Time (Vials)	0	Shifts
38	Secondary Manufacturing Shifts (Vial)	1.0	Shifts
39	Shifts per Week	21.0	
40	Lead Time (Vials)	0.05	Weeks
41			
42	Doses for Syringes	4,707,688	Doses
43	Start Date (Syringes)	23	Week Number
44	Syringe Fill Loss	2.00%	%
45	Syringe Fill/pack rate	215,000	Syringes/Shift
46	Quality Control Lead Time (Syringes)	1	Shifts
47	Secondary manufacturing Shifts (Syringes)	21.5	Shifts
48	Shifts per Week	10.0	
49	Lead Time (Syringes)	2.2	
50			

Table 10: Secondary Manufacturing Input(s) Excel Spreadsheet

Inputs:

Amount of Doses for Vials/Syringes: The amount split between Vials and syringes depends on many other factors that span beyond this model.

Fill Loss: The "required" loss when filling. Novartis is required to provide extra vaccine to compensate for clearing the air from the syringe and the small amount that remains in the vial or syringe even after administered. This ensures the customer receives at least the minimal dose.

Fill/Pack Rate: The amount of vials/syringes filled and packed per shift.

Quality Control Lead Time: See above QC Lead Times

Shifts Per Week: See above Shifts per Week

Output:

Total Lead Time: Simple calculation of how long filling/packing takes.

Production Schedule:

Everything up to this point is used to create a straight forward week by week production forecast.

	Lead Time (weeks)	5.00					
		Monovalent Strain Production			Trivalent Blend Produ	Secondary Manufactu	
Week #		Strain 1 Dur	Strain 2 Dur	Strain 3 Dur	Dur	Vial Fill/Pack	Syringe Fill/Pa
0.5		1,050,000	0	0	0	0	0
1.0		2,100,000	0	0	0	0	0
1.5		3,150,000	0	0	0	0	0
2.0		4,200,000	0	0	0	0	0
2.5		5,250,000	0	0	0	0	0
3.0		6,300,000	0	0	0	0	0
3.5		7,350,000	0	0	0	0	0
4.0		8,400,000	0	0	0	0	0
4.5		9,450,000	0	0	0	0	0
5.0		10,500,000	0	0	0	0	0
5.5		0	3,780,000	0	0	0	0
6.0		0	7,560,000	0	0	0	0
6.5		0	11,340,000	0	0	0	0
7.0		0	15,120,000	0	0	0	0
7.5		0	18,900,000	0	0	0	0
8.0		0	22,680,000	0	0	0	0
8.5		0	26,460,000	0	0	0	0
9.0		0	30,240,000	0	0	0	0
9.5		0	34,020,000	0	0	0	0
10.0		0	37,800,000	0	0	0	0
10.5		0	0	3,150,000	0	0	0
11.0		0	0	6,300,000	0	0	0
11.5		0	0	9,450,000	0	0	0
12.0		0	0	12,600,000	0	0	0
12.5		0	0	15,750,000	0	0	0
13.0		0	0	18,900,000	0	0	0
13.5		0	0	22,050,000	0	0	0
14.0		0	0	25,200,000	0	0	0
14.5		0	0	28,350,000	0	0	0
15.0		0	0	31,500,000	0	0	0
15.5		0	0	0	0	0	0
16.0		0	0	0	2,614,500	0	0
16.5		0	0	0	5,229,000	0	0
17.0		0	0	0	7,843,500	0	0
17.5		0	0	0	10,458,000	0	0
18.0		0	0	0	13,072,500	0	0
18.5		0	0	0	0	0	0
19.0		0	0	0	0	0	0
19.5		0	0	0	0	0	0
20.0		0	0	0	0	0	0
20.5		0	0	0	0	7,714,285	0
21.0		0	0	0	0	0	0
21.5		0	0	0	0	0	0
22.0		0	0	0	0	0	0
22.5		0	0	0	0	0	0
23.0		0	0	0	0	0	0
23.5		0	0	0	0	0	1,048,095
24.0		0	0	0	0	0	2,096,190

Table 11: Production Schedule Excel Spreadsheet

Each cell required an array function to check the week number and how many doses where produced the week before then input the amount of doses produced that week. This model is accurate to a half week. The schedule can be a useful tool in long term planning and determining the timeline between primary and secondary manufacturing. Also despite the lack of new information on the schedule from earlier sections of the model, a schedule does offer a visual element that provides perspective.

6.7 Monte Carlo

Monte Carlo simulations are frequently used in business for risk analysis, decision analysis, and optimization when factors are uncertain. This forecasting method is best utilized when solving complex problems using computer algorithms to simulate the variables. The mathematical algorithm is developed to model the problem and then it is used to run thousands of iterations. This creates a statistical data set that demonstrates the behavior of the model.

One of the skills the group learned from this project was how to take a real world problem and translate into an Excel equation. Fortunately the relationship between the uncertain yield amount and total doses produced is relatively simple.

1	**Model Interaction Variables**			
2	Assumptions			Units
3	Eggs Per shift (E)		400,000	Eggs
4	Total Lead Time (W)		5	Weeks
5	Shifts per Week (S)		21	Shifts
6	Gross Bulk Yield Per Egg (Y)	Min	52.00%	
7		Max	74.00%	
8	*Press F9 to Run a New Simulation*			
9				

Table 12: Model Interaction Variables Excel Spreadsheet

Inputs:

Eggs Per Shift: denoted as **E**

This number will rarely change

Total Lead Time: denoted as **W**

This number is important in trying to determine how long the strain should be run considering the uncertainty of the yield.

Shifts per Week: denoted as **S**

This can be changed to address the demand of a pandemic year compared to an average year.

Gross Bulk Yield per Egg Minimum: denoted as **Ymin**

The historic minimum yield.

Gross Bulk Yield per Egg Maximum: denoted as **Ymax**

The historic maximum yield.

Note: several methods are available to determine the historic minimum and maximum by taking into account the frequency of a high or low average compared to just an unaltered minimum and maximum. This can be determined by the user depending on level of risk.

Algorithm:

E * W * S * Random Number generated between Ymin and Ymax = Total Doses

- The random number generator is essential to a Monte Carlo simulation. Here we used it to generate a yield randomly between the Ymin and Ymax.
- This algorithm is run 10,000 times simultaneously to create a data set.

Frequency Histogram:

After the 10,000 results are calculated, they are put into bins to represent frequency. Then the frequency histogram is created to visually demonstrate the forecasted total dose production.

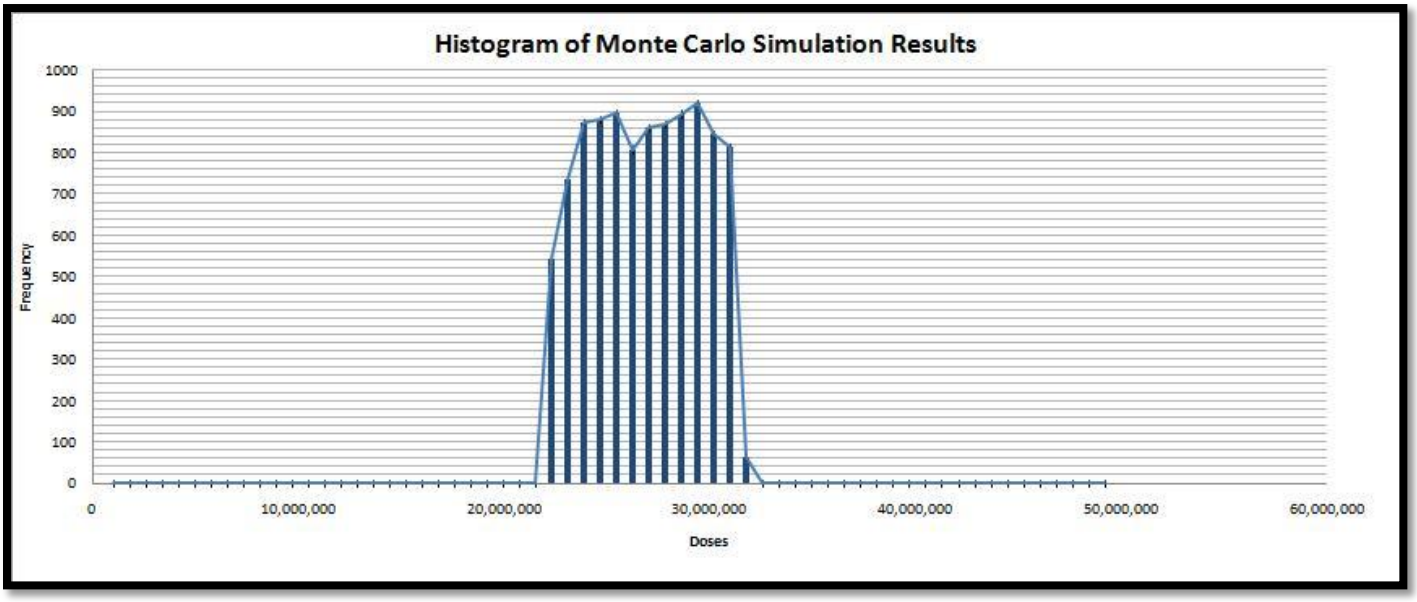

Figure 22: Monte Carlo Simulation Histogram Results

This is an example of a frequency histogram. Ideally the histogram should be narrow and tall to represent less uncertainty in the yield. Also the histogram should be as far to the right as possible to show high production values. Note that the longer production is run, the more susceptible it is to uncertainty. This is illustrated below. The only difference in inputs is Lead Time.

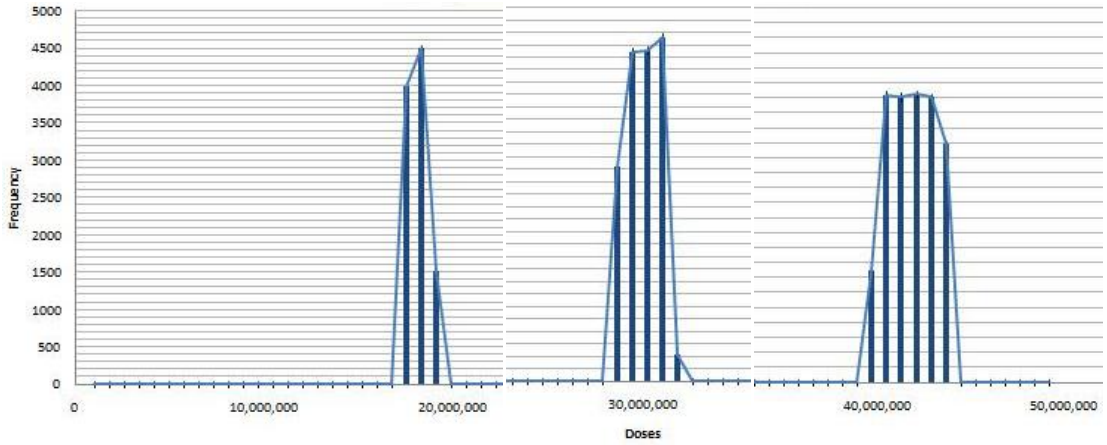

Figure 23: Histogram illustrating higher production values

6.8 Summary Statistics:

In addition to a histogram, a table is generated with valuable statistical data.

Table 13: Summary Statistics Excel Spreadsheet

Outputs:

Central Tendency (Location):

Sample Mean: The average of the sampled data. An estimate of the true population mean.

Median: The Value in the middle of the 50th percentile. Or the average of the middle two numbers.

Standard Error: The uncertainty associated with the estimated mean. The standard error is the estimate of the standard deviation of the sample means for repeated Monte Carlo Simulations and can be used to create confidence intervals.

Spread:

Standard Deviation

Maximum

Minimum

Range: Maximum-Minimum

Third Quartile (Q3): 75th percentile

First Quartile (Q1): 25th percentile

Interquartile Range: Q3-Q1

Shape:

Skewness: If positive, then skewed to the right (longer right side tail) If negative then skewed to the Left (longer left side tail.)

Kurtosis: Peakedness compared to a normal distribution.

Comparisons:

There is a comparison between the 90% interval and the 95% Interval. In addition there is a probability section that shows how probable the true sample mean exists within the given interval or outside of it. Also in a separate box there is the ability to calculate whichever confidence interval desired. This can be particularly useful with risk based decisions.

An example of the formula for a 95 percent confidence interval:

$$\text{Mean} \pm (1.96 * \text{std.dev})/\text{sqrt}\{\text{number of iterations}\}$$

Three strain Monte Carlo Simulation

Since three strains are used for producing a flu vaccine, a Monte Carlo Simulation was created to compare them. The Inputs and outputs are the same but in triplicate.

1	**Model Interaction Variables**			
2	**Assumptions**		**Strain 1**	**Units**
3	Eggs Per shift (E1)		400,000	Eggs
4	Total Lead Time (W1)		5.2	Weeks
5	Shifts per Week (S1)		21	Shifts
6	Gross Bulk Yield Per Egg (Y1)	Min	52.00%	
7		Max	67.00%	
8	**Strain 2**			
9	Eggs Per shift (E2)		400,000	Eggs
10	Total Lead Time (W2)		4	Weeks
11	Shifts per Week (S2)		21	Shifts
12	Gross Bulk Yield Per Egg (Y2)	Min	73.00%	
13		Max	86.00%	
14	**Strain 3**			
15	Eggs Per shift (E3)		400,000	Eggs
16	Total Lead Time (W3)		5	Weeks
17	Shifts per Week (S3)		21	Shifts
18	Gross Bulk Yield Per Egg (Y3)	Min	62.00%	
19		Max	77.00%	
20				
21	***Press F9 to Run a New Simulation***			

Table 14: Model Interaction Variables Excel Spreadsheet

The histograms are overlapped for comparison.

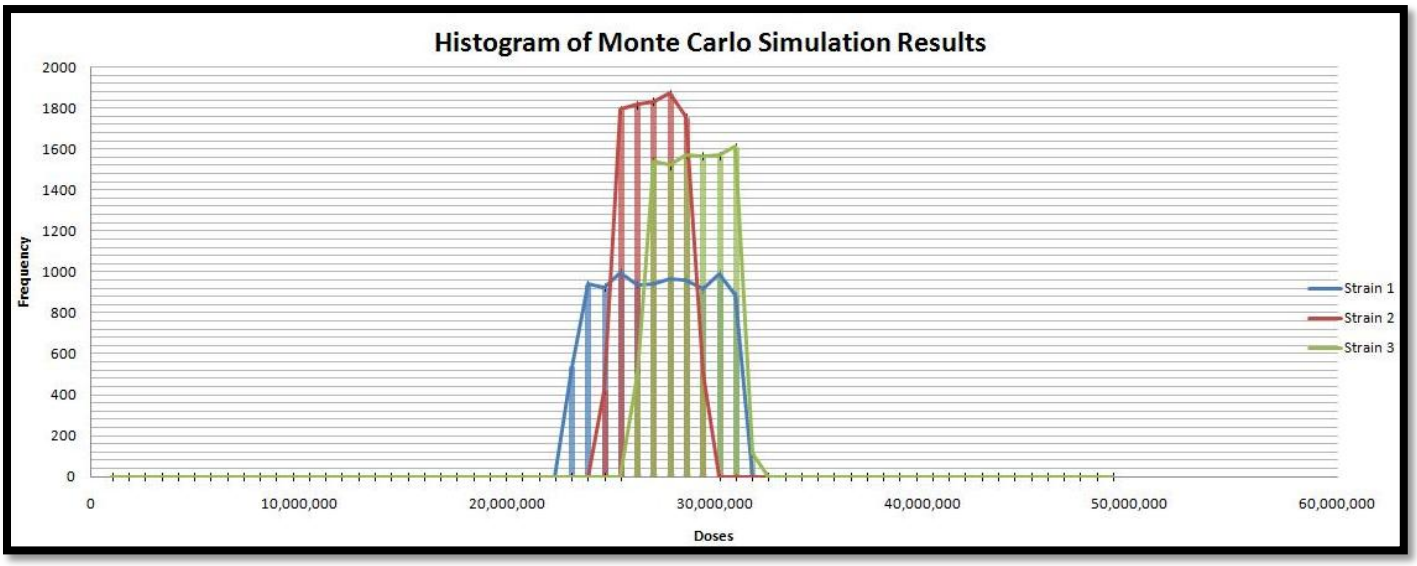

Figure 24: Three varying strains by degree of uncertainty

This first example shows three strains with various degrees of uncertainty however the production lead time was adjusted to have strains produce about the same amount. This will help reduce over production.

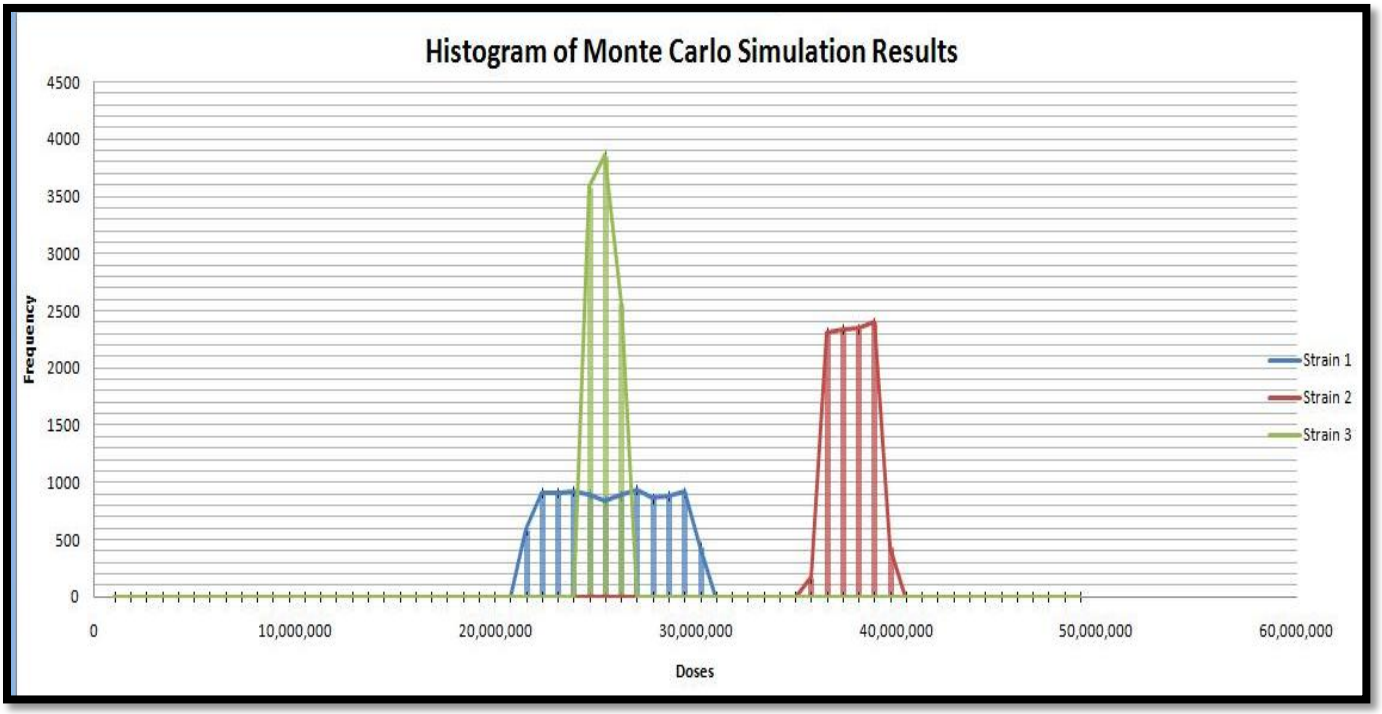

Figure 25: Strains sharing the same sample mean

The second example shows how despite a high uncertainty for strain one and low uncertainty for strain three, they share the same sample mean. However, strain two is being over produced and creating a lot of waste. To fix this, either strain 1,3 need to be produced longer (preferably to increase production) or strain 2 produced for a shorter time (reduce waste).

This simulation also provides a Bubble graph comparison. The size of the bubble shows the spread of the inputted confidence interval (larger bubbles show more uncertainty) and the locations are the minimums and maximums of each confidence interval. Ideally the bubbles should be small, on top of each other and in the upper right corner. The left example shows one that will produce a great deal of waste and one that is closer to optimization.

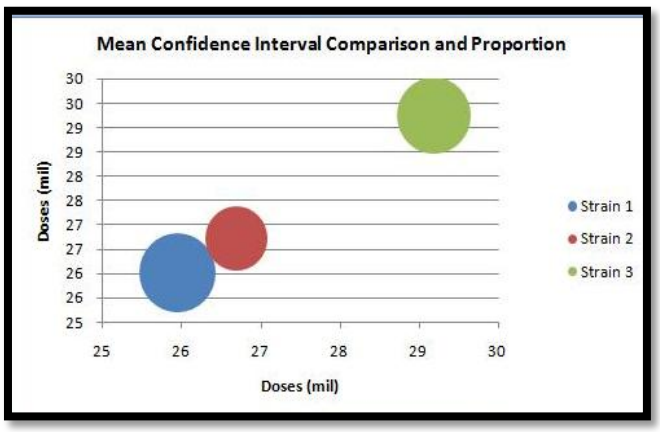

Figure 26: Mean Confidence Bubble Graph #1

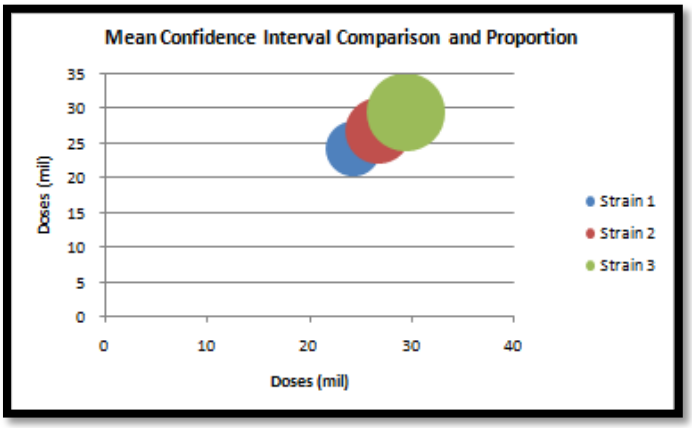

Figure 27: Mean Confidence Bubble Graph #2

6.9 Forecasting Tool Conclusion

This Excel based forecasting model has been tested against historical data and only needs to be implemented into the company where needed. An introduction and how-to section of the model was included to ensure the user has any easy interface. In addition, this model is very flexible can be adapted to new and changing variables or obstacles. Ideally, if a vaccine was produced that would address all strains, then strain forecasting would become obsolete and production can be run all year round. This will increase supply and make the current competitive advantages out of date. Current research is being done to investigate this idea.

7. Recommendations

The recent outbreak of the H1N1 influenza virus has made it clear that vaccine manufacturers must improve their overall manufacturing processes in order to meet market needs. As of 2008, if a pandemic were to break out, existing global manufacturing capacity could only provide sufficient vaccine for about 4.6% of the world's population. Clearly this is a significant issue that must be addressed. Although there are certainly no easy solutions to this problem, there are several new age industry practices that can improve vaccine production efficiency and speed.

One of the most promising developments in vaccine production is the use of cell-based manufacturing in place of the current egg-based approach. The use of Vero cells, which are derived from kidney epithelial cells extracted from the African green monkey, allows for the propagation of viruses in cultured cell lines. Although this method has been used for over 20 years for manufacturing vaccines for polio and rabies, it is a rather new development in influenza vaccine manufacturing. Although the process of cell-based vaccine manufacturing is complicated, the benefits and advantages to be gained from it are very promising. The major advantage of cell-based manufacturing versus egg-based manufacturing is the easy expansion and up scaling in times of emergency such as a pandemic. Additionally, cell-based manufacturing can increase capacity by adding fermentation equipment. Another beneficial aspect of implementing the use of Vero cells is the ability to stockpile. Batches of cells can be frozen and stored, then quickly multiplied when needed. Lastly, cell-based manufacturing data has shown that rapid high-yield production of pandemic vaccine can be achieved in a short time period. This is a particularly important benefit because as we saw with the H1N1 virus low-yielding strains can delay vaccine production. As previously mentioned this is a rather new development in

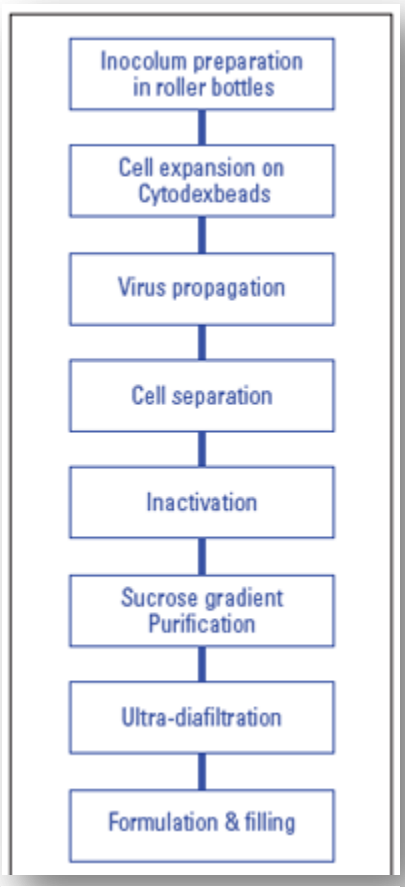

Figure 28: Vero Cell Process

influenza vaccine manufacturing, however the benefits of this approach can result in increased speed and efficiency in flu vaccine manufacturing.

In addition to Vero cells another growing practice in the industry is the implementation of hardware with single-use components. Two of the most significant benefits of single-use components are increased speed and flexibility. Disposable pump heads, bags instead of tanks, and plastic tubing in place of piping result in simpler cleaning and validation processes. Additionally, installation lead times are minimized and equipment can easily be moved around the facility or to other facilities. Implementation of this system also results in minimal downtime and reduced maintenance. Consequently the use of hardware with single-use components also reduces operational costs. It is because of these advantages that implementation of single-use components is gaining popularity in the vaccine manufacturing industry.

In general, there are many new age industry practices that have shown promising results in flu vaccine manufacturing. Vero cells and single-use components are only two of the growing number of practices that can improve overall flu vaccine production. However, implementing these strategies can increase production efficiency and timeliness, which as we know is of dire importance. While implementing these practices is easier said than done, it not only benefits the general public, but it also benefits flu vaccine manufacturing companies. By increasing production capacity and reducing overall lead time companies are more likely to get their product to market first, which will significantly increase the company's sales and profits. In conclusion, the implementation of new age industry practices can provide better protection to the world's population and is therefore beneficial to both the consumers and the corresponding vaccine manufacturers.

8. Capstone Insights

8.1 Identification

Definition:

"Engineering Design is the process of devising a system, component, or process to meet desired needs. It is a decision-making process (often iterative), in which the basic science and mathematics and engineering sciences are applied to convert resources optimally to meet a stated objective. Among the fundamental elements of the design process are the establishment of objectives and criteria, synthesis, analysis, construction, testing and evaluation" (ABET).

Objective:

The goal of the project was to create a mathematical model that acts as a tool to better forecast the production and scheduling of the Flu vaccine manufactured by Novartis vaccine and Diagnostic.

Criteria:

The mathematical forecasting tool was to have several requirements that were known before construction began. The first criteria was that it the mathematical model be an easy-to-use program that would simply forecast the amount of doses in the manufacturing phase at any given point in time. The second criterion was that the program be able to compose a schedule and generate specific numbers throughout the course of the manufacturing year. The final criterion was to use a software program that was easily accessible on most computers to reduce costs of having Novartis needing to buy new software licenses for the company infrastructure.

Synthesis:

Throughout the course of the project we were able to combine multiple forms concepts of math and science. Our team began by utilizing the science behind vaccines and their

characteristics of materials to get a better understanding of how they are produced. Through principles of supply chain management and manufacturing techniques, we as a team were able to combine that with the science behind the vaccines in order to better forecast the production quantities. It allowed us to create a time scale and generate rates of production per month accordingly.

Analysis:

The important part of the forecasting model was the analysis of previous material such as models used in the past to generate and produce certain equations and numbers. We were given a multitude of excel files that were based on individual parts of the flu vaccine production process. We were able to break each program down into the basic math and science formulas to understand how each item and output were calculated. From there we were then given a set of historical data from previous manufacturing cycles to test the formulas to insure accuracy.

Construction:

An in-depth comprehension of the flu vaccine production and supply chain decisions where necessary in the development of the forecasting model. The creation of an end to end supply chain map was invaluable in understanding the complexity and numerous variables affecting the production process.

Another obstacle that was addressed in the early stages of development was the exact purpose and use for the model. It is not uncommon for clients to have a very vague idea as to what the end result of the product should accomplish. This obstacle was overcome by following the System Development Life Cycle (SDLC) used by Management Information System software programmers and designers.

Each phase (up through the Integration and Testing phase) was addressed by posing relevant questions to the Novartis contacts and systematically acquiring the information and data required to

move from one phase to another. This allowed the team to more accurately address the core need and narrow down the scope from a broad and vague concept to a narrow and practical model.

Testing and Evaluation:

After the final product was constructed and completed it entered into a testing and evaluation phase. This consisted of entering in historical data. By doing so, this enabled us to determine if the program indeed was running correctly. We were able to enter the data, run the various simulations, and compare the outputs from our newest program to the outputs generated in the historical data from past programs.

8.2 Alternatives and Constraints

Health and Safety:

The second constraint we came across was health and safety. This applies directly to Novartis's supply chain and manufacturing processes. More specifically, eggs. In the manufacturing process for the antigens, the flu virus is injected into the egg and antigens are allowed to grow within the egg. The health and safety issue is that thousand of eggs are bought and only a percentage of the eggs are used. This is due in part to the eggs being bad or having flaws. Novartis would be able to produce a significant amount more antigen material if they received one hundred percent flawless egg material.

Sustainability:

The next constraint was sustainability. For the program to remain in line with production is not exactly feasible. The manufacturing process is always changing with the new addition and subtraction of specific production steps by process engineering specialists. The process is ever

growing and in the future the program will need to be modified to accept these new changes that lead to new input constraints such as eggs per day or strain yields.

Manufacturability:

The manufacturability plays an important role in the pharmaceutical industry, especially when dealing with strain yield. There is an uncertainty of strain yields from year to year and strain to strain which causes a hiccup in the beginning production processes. Also quality control is very important and depending on the place its going drastically increases lead time. If everything needs to be going through quality control at every error or process change it all adds up in lead time.

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Appendix A

Meeting Minutes

Novartis Supply Chain Management Team
Meeting Minutes – Department of Management Conference Room
9:00am – 25 September 2009
Attendees: *Dan Cafferty, Drew Sansevero Marc Chatterton, Dave Gardner, Jodi*

I. Question/Answer

a. In the end you would like a "User friendly package" to help understand the opportunities given by the supply chain we create. What exactly would you like this package to consist of so we can make an outline of goals and objectives?

There are all kinds of process maps and people at Novartis that understand the basic processes. There is no way of predicting what strain will be released to the company. If Novartis received the reagents a week early they could get the product to the market faster and the better off the company can be competitive wise. Last year's goal was that by the end of August to get as much volume out to the market in order to obtain the best contract. Now it is a matter of after the map and components are assembled how they can use our tool to focus and use on forecasting. The yields are unknown until Q1 of each year. This model should be able to be used at any given point of time in the year to determine, for example, the number of doses instantaneously in the system.

b. Is there a specific software program you would like us to use in mapping the supply chain and determining certain parameters?

We will be using Microsoft Visio to map out the supply chain processes.

c. Are we sure that there is no already existing supply chain end-end map?

Jodi will be sending us a high level map of the basic process for the strains and the different organizations involved in the supply chain processes.

d. Can we get a basic process of how a flu vaccine is manufactured in the build process?

In the Liverpool manufacturing department, 450,000 eggs per day are used to make the product. The virus is injected (inoculated) into the eggs. The World Health Organization supplies companies worldwide with the virus strains which are told by the WHO that they are to use each year. The virus is then allowed to grow and replicate within the chicken eggs for certain periods of time. The embryo is then killed and the fluid that contains the replicated virus is harvested off. It looks like a ball with spikes coming off of it. The spikes are the antigens and they are the only part needed. They trigger the immune response for the flu

virus. Fluverine has a vial process line as well as a syringe line. Some product is shipped to Italy for a filling line. QC testing occurs as the product is running. Every step of the process has to be recorded because this is being injected into people's bodies. Deviations must be recorded and the deviations per batch must be authorized by the government that it is being sent to. Liverpool creates virus, fills it halfway, and then ships to Italy for final filling and packaging.

Novartis Supply Chain Management Team
Meeting Minutes – Department of Management Conference Room
9:00am – 1 October 2009
Attendees: *Dan Cafferty, Drew Sansevero, Dave Gardner*

II. General Discussion

a. Overall Warehouse Strategy – Liverpool ,UK

There is a Good Manufacturing Practices (GMP) warehouse in Liverpool that stores in process material that will be filled. This is Novartis's intermediate supply. For Germany, the products are only formulated and then sent to a third party supplier called Catalent (filling, inspecting, and packing). The number of warehouses varies from country to country but there is no centralized warehouse or distribution center. Another third party residing in Spain called Rovi is used as an overflow backup warehouse.

III. Question/Answer

e. No formalized communication with entities that develop seeds with better yield characteristics. Do you have any strategic alliances or partnerships with these third parties?

No update developing formalized communication with entities that produce a better yield. The strategy is to have a better relationship with third party suppliers or partnerships. In general, these relationships have improved from the past. These relationships help in predicting the strain which in time gets supplies to the production lines faster. Novartis is continuing to nourish this relationship.

f. In terms of the Push-Pull technique, do you still continue to only work with a primarily push type of system or has it changed?

It is still primarily a Push system. However there is a pull system for antigen manufacturing and a push system for secondary manufacturing (syringes and viles). In the future there is the possibility of obtaining a hybrid push-pull system. The commercial operations department at the beginning of the year says they will sell a certain amount, for example 40 million doses. Then manufacturing says they will make 40 million doses. If operations backs off the 40 million and goes to 30 million, 10 million is wasted. Pull system could be then in effect and be more efficient. Only problem is the short window of time. The company wants to work towards realistic demands based on past predictions of past yields. Make batches based off

previous projections. Hold certain amount of in process inventory. They could initiate a kanban system. As long as each singular strain isn't formulated in a final product, those strains could be held over multiple years and if they get lucky they will be used the next years possibly. Company could make "x" number of doses, as soon as its ready run like crazy and formulate everything. The strains usually last and then expire after 3 years. As soon as you know what strains are, manufacturing begins.

g. Any changes with improving batch release times by changing the quality control system?

Current way put manufacturing back 3 weeks and it is still the same. There is a lot of emphasis on changing the current QC system because of the recent swine flu. This is the same for the operations and manufacturing business for seasonal flu as well. Release process is holding up the final product until authorities give the okay. There are a few key things that impact release. Every step of the process must be documented. Includes QC testing of final product and that could hold it up from being released. Deviation management process holds up most of the time in the system. Anytime something goes out of specification or there is an error in the batch record, root cause must be developed and then a corrective action is put in place to close out the deviation report. Every deviation needs to clear before the final product can be released. This varies from holding up a small batch (3 weeks) to also holding up entire batches (9-10) weeks.

Current: production is documented and quality does a review. If there is an issue, QC gives back to manufacturing. Recently converted this process to real time, in that QC is now on the production floor to eliminate process times.

h. What is the percentage of sales and production for swine flu?

About 50-70% of the business is flu vaccines. Novartis does not want to rely solely on flu products for profits. Instead they are investing a lot of revenue in the meningitis franchise. Until the new meningitis products are launched, the flu vaccines are driving Novartis's main source of business and revenue.

Novartis Supply Chain Management Team
Meeting Minutes – Department of Management Conference Room
2:00pm – 13 November 2009
Attendance: *Dan Cafferty, Drew Sansevero, Marc Chatterton Dave Gardner*

IV. General Discussion

b. Key Topic to Focus On

Forecasting. Anything that will allow us to input parameters to forecast out what they could expect o also help us to scenario plan. If they were able to increase strain, over a month by month process how many doses are going to be available?

Mark Hope was contacted to help us out during our conference calls. He has created value stream maps that will be sent to us soon to evaluate the processes more in depth and also to be able to gain more data variables for creating a program.

Wild seed strain and non-profit organization are trying to make a better yielding value. Swine flu is a totally new and unique strain that no one has seen before

c. Mathematical Program Concepts

- Strain Type
- Historical Yield
- Eggs Utilized
- Transportation Time

Leave out historical yield and allow the program users to input the yields. Take one strain and coat into the program. Users need to be able to go in and change the yield.

Manufacturing is identical between seasonal flu and H1N1. The only minor difference is that the H1N1 does not produce as much antigens then the seasonal flu produces.

All egg based manufacturing will be performed at Liverpool. In 2013 they want to cut costs from Italy. They will also be consolidating secondary operations in Italy as well.

V. Question/Answer

i. Previous MQP?

There have been other previous projects done by other intern students but they have not been related in our field for this project. However, there is a consultant who has done excel work in spreadsheets that is very complicated but if we look deep into the calculations we will be able to determine how it works.

j. Is the capacity planning model up to date?

No particular model they use and that is the main problem. Intern did one time snap shot analysis and in no point in time did they have a tool they could utilize. H1N1 has addition tracking and a lot of data specific to one strain. Nothing proactively to use to ay this is the result we are going to get. Strains are unknown until February, so unknown what you can get from a yield standpoint. They want something they can easily make changes and be flexible in case strain types change. "This has been run in the past so the yield then was XYZ

Primary and secondary are the main processing types. Primary is the bulk. Eggs go in and antigens come out. Secondary is filling and finishing the vials and syringes.

k. Software to use?

MS Visio is used by Novartis to value stream map the processes. Excel based program is being used for modeling yields. Want to use a Monte Carlo technique to approach this project. Most people in the company will only have excel so

l. Additional Meeting Time for our group every week?

Tuesdays 9am
Fridays 2pm

Novartis Supply Chain Management Team
Meeting Minutes – Department of Management Conference Room
9:00am – 17 November 2009
Attendance: *Dan Cafferty, Drew Sansevero, Marc Chatterton, Mark Hyde*

VI. General Discussion

d. Recent Progress

We have downloaded and installed Microsoft Office Visio Studio. Dave gave us several different value stream maps and we have begun to try and figure out how to make one "master" value stream map combining these sub level maps he has sent to us. We started cutting them out and piecing them together and our next step is to insert these paper maps into Microsoft Visio as an electronic version.

VII. Question/Answer

m. List of suppliers for reagents, eggs, etc.?

The main supplier is T.K. Woods. They have multiple farms and supply Novartis with 471,000 eggs per day, but the site license only allows harvesting up to numbers of 400,000 eggs per day. The only other main products that Novartis outsources are tubing and hardware. The length of the supply chain is very minimal because most processes are done in house.

n. What do the terms upstream and downstream refer to?

Downstream is live virus and upstream is terminating it and purifying it. Mark Hyde will be sending us addition documents with all of the terminology that is used in Novartis's process and documentation.

o. Anymore insight on yields and numbers available for us?

25%-35% yield per season. Came out to close to what was required by the constraints. There will be a tab in the program to allow the user to insert or edit the yields. For now, we would like to make the program as simple as possible and have the user have to insert as least amount of information as possible. However we realize there are variables that change over periods of time so they will be able to go in and change whatever we place in the program as constants at given times.

p. Any historical yields available to us (i.e. past 5, 10, 20 years)?

Mark Hyde will get this information to us for next time.

q. What is the shelf life of the antigens before it is mixed?

Mark Hyde will get more technical information to us. Once it goes into a vile it has a stability shelf life that is designated for the customer. They take an educated guess at the start of the year for the first number of batches but if wrong it can be a billion dollar bet and possible loss of licensure.

r. What variables would you like to see in the final program/simulation we build?

A lot of lead times are QC times that are not seen and may want to take note of and hold accountable in our model. Some lead times include 14 day time periods.

s. Final "Shopping List" for Mark Hyde to work on obtaining for our project:

1. Shelf life of antigens before they are mixed
2. Historical yields from the past 5, 10, 20 years
3. List of suppliers
4. Terminology/Vocabulary file for Novartis's processes

Novartis Supply Chain Management Team
Meeting Minutes – Department of Management Conference Room
9:00am – 01 December 2009
Attendance: *Dan Cafferty, Drew Sansevero, Marc Chatterton, Dave Gardner, Mark Hyde*

VIII. General Discussion

e. Recent Progress

The first draft of the value stream map will be done by Wednesday morning. We will send to Dave Gardner and Mark Hyde to have it edited and revised. A first draft tool has been created in excel and is in the process of being "tweaked".

IX. Question/Answer

t. For the forecasting tools do you prefer days or weeks for units?

Either weeks or days will work. Days however is more granular.

u. For the yield, they subtracted yield from a base case?

Not the best way to do it. When the yield is factored in, it typically is accounted for in doses for eggs. For non-egg based they look at grams per batch. There is a push for using grams in Liverpool but for this project we will focus on using doses per eggs.

v. Are you taking yield percentage and multiplying it by eggs?

For the most part if an average is known they can get one dose per egg. In theory each day they have the ability to generate 450,000 doses per day. However it reduces itself from losses, overages, overfills, etc.

w. Calculate loss in percentage?

Work has been done in the last several weeks in Liverpool for each phase of centrifugation, splitting, and purification. It will be added to this week's shopping list.

x. Strain with the lowest number is maximum doses produced (i.e. constraint)?

That is a constraint in the forecasting tool. If one strain only yields half of another strain, they obviously will run the strain twice as much. Once they get into the latter part of the year in a non-pandemic situation, they will produce extra antigens for predicting next year's strain from the NON-blended supply. If for example 30 million trivalent blends are sold off and an extra 10 million doses ARE blended and not sold off, they are scrapped.

y. Recent "Shopping List" for Mark Hyde and Dave Gardner to work on obtaining for our project:

1. Data for loss percentage calculations.

Appendix B

CONFIDENTIALITY AGREEMENT

THIS AGREEMENT is made effective as of _____, by and between Novartis Vaccines and Diagnostics, 350 Massachusetts Avenue, Cambridge, MA 02139 ("Novartis"), and Worcester Polytechnic Institute, having its principal place of business at 100 Institute Rd., Worcester, MA 01609 ("WPI"), as set forth herein.

1. Confidential Information; Purpose. This Agreement concerns the disclosure by each party (each a "Discloser") to the other party (a "Recipient") of information of a confidential or proprietary nature, whether oral or written, that is not generally known outside of the Discloser, including but not limited to information relating to the Discloser's products, designs, methods of manufacture or research or to the Discloser's business operations such as its marketing plans, customer lists and pricing methods as well as its personnel and organizational data, relating to projects conducted to improve/model the various supply chain and energy consumption processes and/or systems across the company (all such information, each party's "Confidential Information") in connection with, but not limited to, the parties' discussions relating to modeling the company's supply chains and/or energy consumption.

2. Confidentiality and Use Restrictions. Recipient shall maintain Discloser's Confidential Information in confidence. Recipient shall use Discloser's Confidential Information solely in connection with the Purpose, unless otherwise mutually agreed in writing. Upon request by Discloser, Recipient shall return all of Discloser's Confidential Information provided hereunder, including any copies thereof, except that one (1) copy of the written materials may be retained by the Recipient for purposes of verifying compliance with this Agreement. Recipient shall confine its dissemination of Discloser's Confidential Information only to those of its Affiliates or individuals within its organization or its consultants who have a need to evaluate the information for the performance of the Purpose and who are bound to obligations of confidentiality and non-use at least as strict as those contained herein. For the purposes of this Agreement, "Affiliates" means any entity that is controlled by, controls, or is under common control with Recipient. For such purpose the term "control" means (a) direct or indirect ownership of more than fifty percent (50%) of the voting interest in the entity in question, or more than fifty percent (50%) interest in the income of the entity in question; provided, however, that if local law requires a minimum percentage of local ownership, control will be established by direct or indirect beneficial ownership of one hundred percent (100%) of the maximum ownership percentage that may, under such local law, be owned by foreign interests; or (b) possession, directly or indirectly, of the power to direct or cause the direction of management or policies of the entity in question (whether through ownership of securities or other ownership interests, by contract or otherwise).

3. Exceptions. Recipient's obligations hereunder shall not apply to any part of the disclosure which: (a) is or becomes publicly known other than through breach of this Agreement by Recipient; (b) is received by Recipient in good faith from any third party not under obligation of confidentiality to the Discloser; (c) is in Recipient's rightful possession on a non confidential basis prior to disclosure by Discloser hereunder; (d) is independently developed by Recipient as evidenced by contemporaneous written record; or (e) Recipient is required to divulge either by a court of law or in order to comply with any federal, state or local law or regulation (after providing Discloser with reasonable notice of such requirement to divulge and with an opportunity to obtain a protective order). For the avoidance of doubt, any disclosure made to the regulatory authorities shall not terminate the confidentiality obligations of the present Agreement.

4. Property of Discloser. Recipient agrees that Discloser's Confidential Information shall at all times remain the property of Discloser. Discloser represents and warrants that the disclosure of the Confidential Information to Recipient does not violate the rights of any third party. Nothing in this Agreement shall be construed as a license or grant to Recipient by Discloser of any patent or other rights in or arising out of Discloser's Confidential Information.

5. Term. This Agreement and Recipient's obligations herein shall remain in effect for a period of seven (7) years from the effective date indicated above.

6. Assignment. This Agreement may not be assigned or transferred without the prior written consent of both parties, which consent shall not be unreasonably withheld; *provided*, *however*, that either party may assign this Agreement to any person or entity which acquires all or substantially all of its business or assets (or of the business division or product line of such party to which the Confidential Information primarily relates).

7. Governing Law. This Agreement shall be governed and construed in accordance with the laws of Italy without regard to its choice of law principles. The courts of Siena, Italy shall have exclusive jurisdiction over any disputes arising out of or in connection with this Agreement.

Entire Agreement; Modification. This Agreement is the entire agreement between the parties with respect to the subject matter hereof. This Agreement may not be amended, modified or released except by a written instrument signed by an authorized representative of each party.

IN WITNESS WHEREOF, authorized representatives of the parties have executed this Agreement on the dates set forth below.

NOVARTIS VACCINES AND DIAGNOSTICS

_____

Name: David Gardner

Title: Head of Operational Excellence & IQP

Global Technical Operations

Date: _____

Worcester Polytechnic Institute

_____

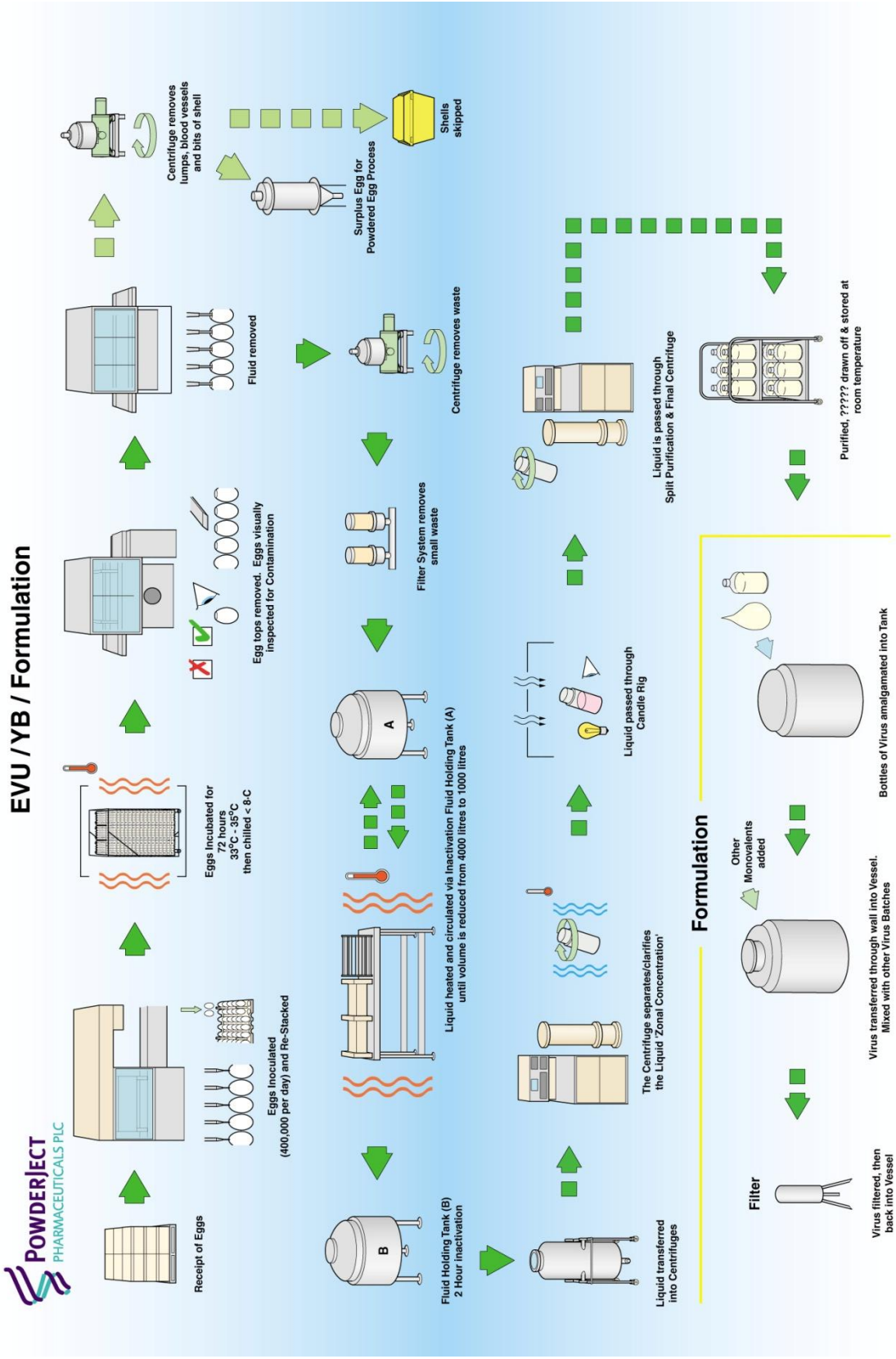
Name:

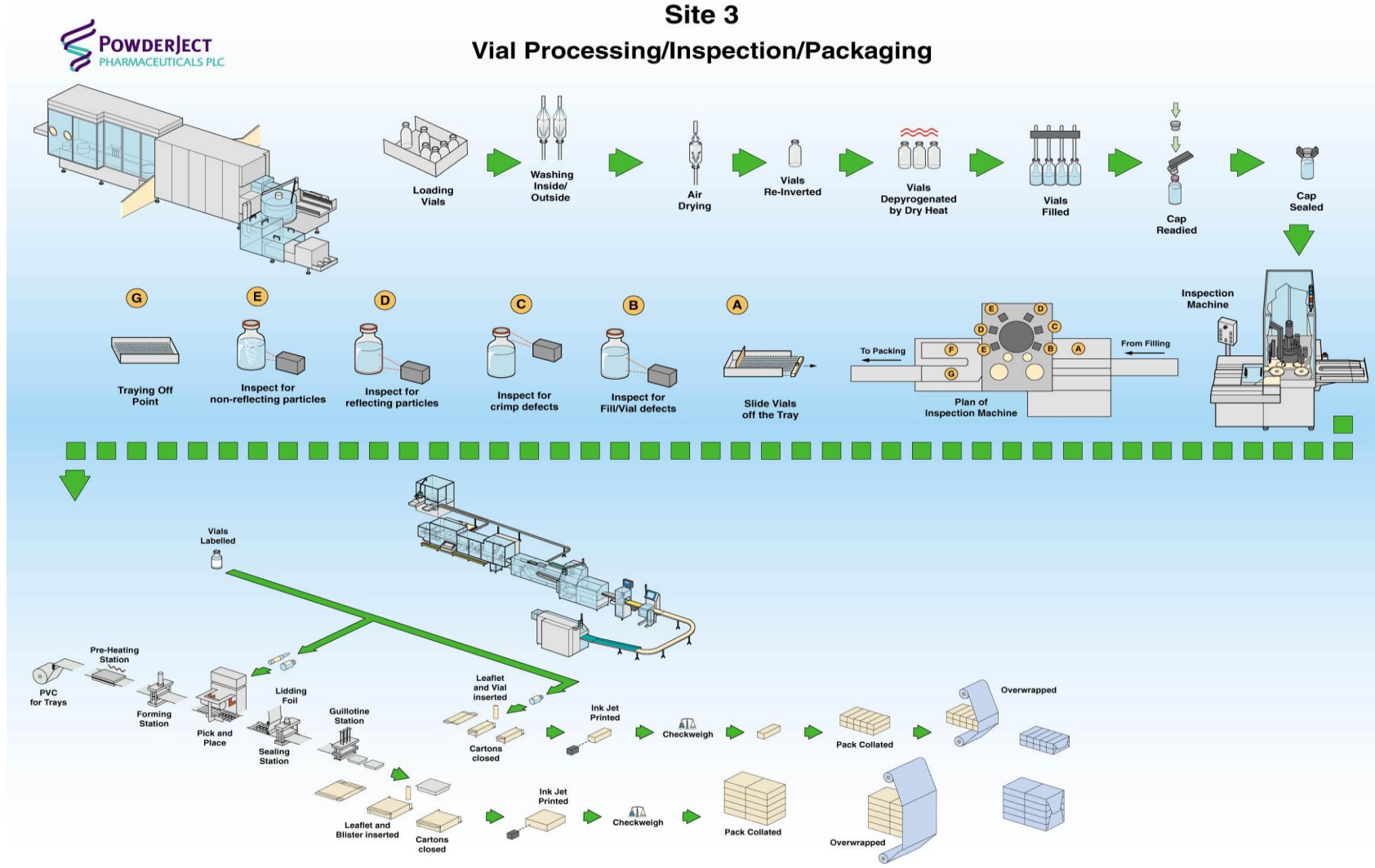
Authorized Representative

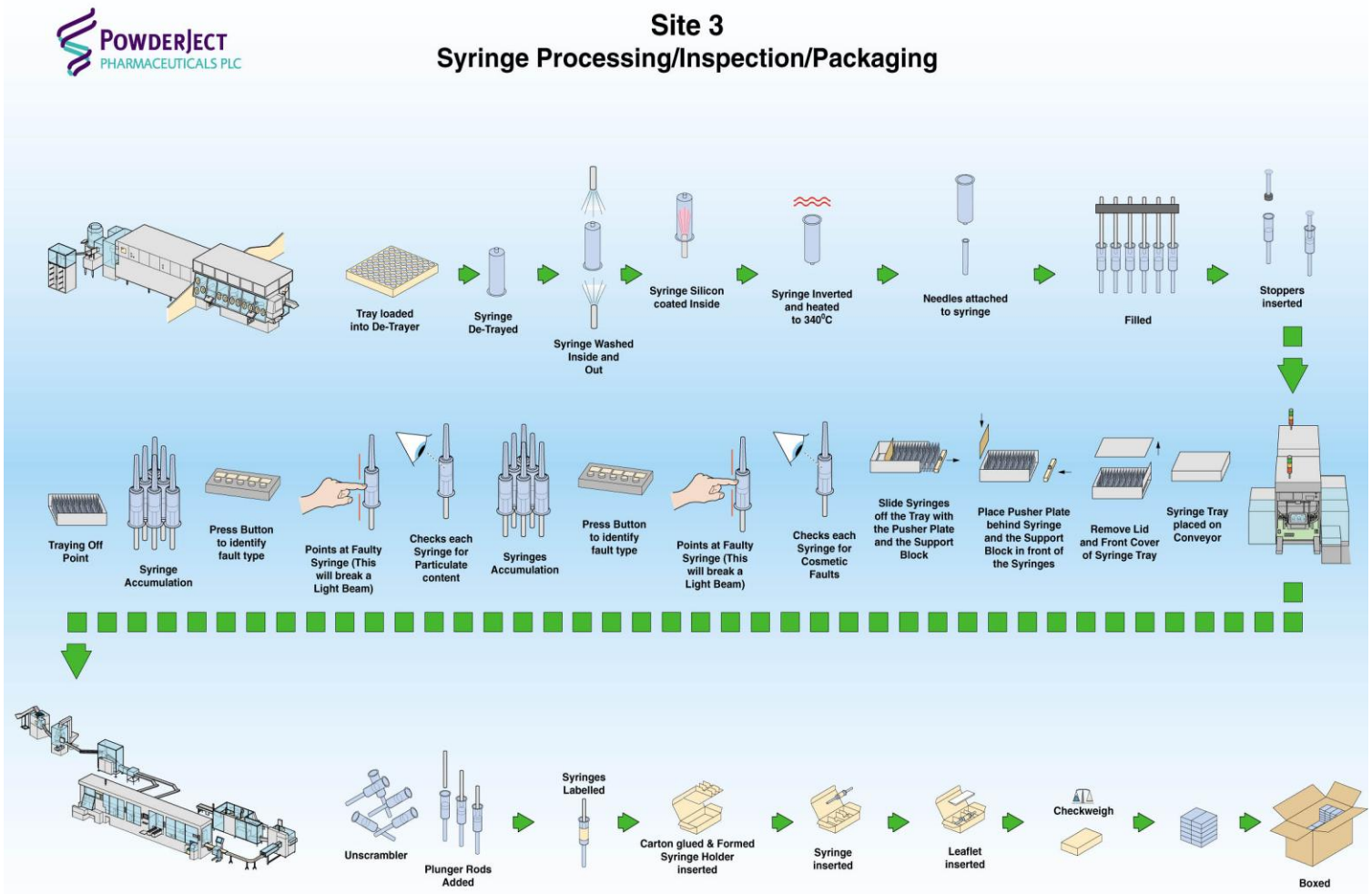
Date: _____

Appendix C

Flu Process Flows




POWDERJECT
PHARMACEUTICALS PLC
Site 3
Vial Processing/Inspection/Packaging
Loading Vials
Washing Inside/ Outside
Air Drying
Vials Re-Inverted
Vials Depyrogenated by Dry Heat
Vials Filled
Cap Readied
Cap Sealed
Inspection Machine
G
E
D
C
B
A
Traying Off Point
Inspect for non-reflecting particles
Inspect for reflecting particles
Inspect for crimp defects
Inspect for Fill/Vial defects
Slide Vials off the Tray
To Packing
From Filling
Plan of Inspection Machine
Vials Labelled
PVC for Trays
Pre-Heating Station
Forming Station
Pick and Place
Lidding Foil
Sealing Station
Guillotine Station
Leaflet and Blister inserted
Cartons closed
Ink Jet Printed
Checkweigh
Pack Collated
Overwrapped
Leaflet and Vial inserted
Cartons closed
Ink Jet Printed
Checkweigh
Pack Collated
Overwrapped


POWDERJECT
PHARMACEUTICALS PLC
Site 3
Syringe Processing/Inspection/Packaging
Tray loaded into De-Trayer
Syringe De-Trayed
Syringe Washed Inside and Out
Syringe Silicon coated Inside
Syringe Inverted and heated to 340°C
Needles attached to syringe
Filled
Stoppers inserted
Traying Off Point
Syringe Accumulation
Press Button to identify fault type
Points at Faulty Syringe (This will break a Light Beam)
Checks each Syringe for Particulate content
Syringes Accumulation
Press Button to identify fault type
Points at Faulty Syringe (This will break a Light Beam)
Checks each Syringe for Cosmetic Faults
Slide Syringes off the Tray with the Pusher Plate and the Support Block
Place Pusher Plate behind Syringe and the Support Block in front of the Syringes
Remove Lid and Front Cover of Syringe Tray
Syringe Tray placed on Conveyor
Unscrambler
Plunger Rods Added
Syringes Labelled
Carton glued & Formed Syringe Holder inserted
Syringe inserted
Leaflet inserted
Checkweigh
Boxed

Appendix D

Title: Process Description of Upstream Manufacturing for Aflunov (H5N1) in Liverpool Site 4

Areas Covered: Operations - Upstream Manufacturing Site 4

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STAG				
Site 4 Head				
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Executive Summary

The Primary Manufacturing process for the Agrippal platform and derivative products (seasonal and pandemic), will be transferred from the Novartis Vaccines and Diagnostics (NVD) facility in Siena, Italy to the NVD facility in Liverpool, United Kingdom (UK).

Aflunov is an influenza pandemic vaccine, surface antigen, inactivated, adjuvanted with MF59C. It contains purified haemagglutinin (HA) and neuraminidase (NA) surface antigens similar to those circulating on the surface of the most prevalent pandemic H5N1 strain. Individual influenza virus strains are individually grown in embryonated chicken eggs, harvested and inactivated by formaldehyde treatment before purification of the surface antigens and formulation with the MF59C.1 adjuvant. The use of Aflunov is recommended in the intra-pandemic periods.

This document will describe the process to be transferred for primary incubation and upstream manufacturing of Aflunov (H5N1) at the Liverpool site. It includes overall operating conditions, objectives, sampling requirements, equipment used, input and output streams, critical/key parameters monitored, filter integrity test requirements and any key decisions.

Note: This document describes control parameters for the Aflunov process. Definitions of key and critical parameters related to the Aflunov process are described in the Process Comparability Plan.

Discussion

2.1 PIU Operations

The goal of this step is to receive fertile hens eggs from accredited suppliers to the Novartis primary incubation facility for exterior washing, primary incubation and candling.

Note: Egg supply and handling of eggs prior to receipt by PIU is described by the associated supplier agreement.

2.1.1 Egg Delivery

Eggs are received in racks on trolleys at Novartis' primary incubation facility (PIU) from vendors. During transportation eggs are held within a temperature range of 12 - 18ºC, and above 50% RH. Eggs are removed from delivery trucks into a cold storage area within the PIU facility to await exterior washing. The temperature of the cold storage area is 12 - 18ºC (target temperature 16ºC) and above 50% RH (target 75%). The eggs can remain in the cold storage area for up to 7 days.

Once eggs have been delivered from the supplier's delivery wagon, the wagon is cleaned using the approved monthly rotational disinfectant according to procedure.

2.1.2 Egg Wash

Egg trolleys are removed from the storage room and rolled up to the MS Technologies washing machines. Egg trays are removed and conveyed along the washer. Each tray is washed in three stages: 1) Chlor-wash: minimum available chlorine > 200 ppm at 44 ± 3ºC; 2) Chlor-wash: minimum available chlorine > 200 ppm at 48 ± 3ºC; 3) QUAT 800 (quaternary ammonia based cleaner): minimum QAC 300 ppm at 49 ± 3ºC. Eggs are re-racked onto trolleys and allowed to dry at room temperature for a minimum of 2 hours.

2.1.3 Primary Incubation

Once the eggs have dried, the trolleys are rolled into incubators. The eggs are incubated between 10 and 12 days (target duration, 11 days) at 37.0 ± 1.0ºC (target 37.5ºC) and 55 ± 10% RH. Eggs are regularly turned during primary incubation.

2.1.4 Candling

Once the eggs have completed primary incubation, trolleys are removed from the incubators and rolled into the candling area. The automatic candling machine is calibrated at the beginning of each production day using a tray of manually candled eggs. Trays are conveyed along the candling machine where each egg is held against a fiber optic light source. Eggs which are infertile, moribund or non-viable are rejected based on light transmission. The candling machine runs at a rate of 8 trolleys per hour.

In addition to the automatic candling machine, one random tray of eggs per trolley is removed to a dark room for manual candling. Rejection of trays and trolleys is performed per AQL procedure. Open tray spaces left from rejected eggs by either automatic or manual candling are replaced with viable eggs. (Note: eggs are backfilled from a single flock code, eggs cannot be backfilled from different flock codes.)

2.1.5 Warm Room

Once candling is complete eggs trays are reloaded onto trolleys and temporarily placed into a warm room to await transport to site 4. The warm room temperature range is 28 - 38ºC, (target temperature 33ºC), there is no humidity control in the warm room. Eggs may be kept in the warm room for a maximum of 4 hours, per procedure. From the warm room trolleys are loaded into a truck 8 at a time and transported from PIU to Site 4.

2.2 Site 4 Egg Receipt

The goal of this step is to receive washed, pre-incubated, candled eggs from Novartis' primary incubation facility to the Site 4 primary manufacturing facility. Eggs are inspected to ensure no damage has occurred during transport from PIU to Site 4.

2.2.1 Egg Receipt

Eggs are transported from PIU to Site 4 via delivery wagon. Eggs arrive in the egg receipt area of Site 4 and are placed into a hold area for inspection. If, for any reason, the eggs are not off-loaded within 1 hour the eggs are sent back to PIU to be held in the warm room. All trolleys are visually inspected for damage which may have occurred during transport. Rejected trolleys are segregated in the PIU Return Room then returned to PIU, per procedure. Accepted trolleys move forward for candling and inoculation.

The delivery wagon is cleaned and disinfected regularly per procedure using the monthly rotational disinfectant.

2.2.2 Candling

Once the eggs have been accepted, trolleys are removed from the hold area and rolled into the inoculation area. Three trays are randomly selected from each trolley, (minimum 5.2% of received eggs) and are removed to a dark booth for manual candling. Each egg is held against a fiber optic light source. Eggs which are infertile, moribund or non-viable are rejected based on visual inspection of light transmission. Rejection of trays and trolleys is performed per procedure. Eggs which are cracked, have an irregular location of the allantoic cavity, double yolks or bloodspots revealed during candling are also rejected.

Once candling is complete eggs trays are reloaded onto trolleys and continue for inoculation.

2.3 Inoculation

The purpose of this step is to inoculate prepared flu virus into the allantoic cavity of embryonated chicken eggs to allow virus replication.

2.3.1 Inoculum Preparation

Virus inoculum is a prepared dilution of the working seed, PBS buffer pH 8.0 and antibiotic solution. All connections are made under laminar flow conditions, transfers are made using sterile pipettes, Nunc tubes and Nalgene bottles and environmental monitoring is performed during these transfer / preparation activities.

A 200 L bag / pallet tank containing 120 L of sterile PBS buffer pH 8.0 is brought into the area, with the seed addition line wiped down and brought under the laminar flow cabinet. 60 mL of sterile antibiotic solution is pumped into the PBS buffer using a peristaltic pump. The antibiotic solution consists of kanamycin acid sulfate, neomycin acid sulfate and PBS buffer pH 8.0. The solution uses the following composition per 1 mL: 50 µg kanamycin, 25 µg neomycin and qs to 1.0 mL with 0.01M PBS buffer pH 8.0.

Simultaneously, a 1000 mL bag of sterile PBS buffer pH 8.0 is brought into the area and placed in the laminar flow hood. 600 mL of the buffer is transferred to a Nalgene bottle and 0.3 mL of sterile antibiotic solution is transferred into the PBS buffer. The resulting PBS / antibiotic solution is dispensed into additional containers according to procedure to perform the appropriate dilution from the working seed. Dilution ranges between 10^{-4} to 10^{-9}. Working seed is provided in vials containing 0.5 mL of working seed.

Once the inoculum dilution has been prepared, the Nalgene bottle containing the seed is connected to the seed addition line of the 200 L bag / pallet tank of antibiotic / PBS buffer. The seed is pumped into the bag and then re-circulated to mix via peristaltic pump. One 120 L bag of inoculum is prepared for each batch.

2.3.2 Inoculation

Site 4 utilizes two Embrex EB132 egg inoculation machines for virus inoculation.

The Embrex EB132 egg inoculation machines are cleaned and prepared prior to inoculation start. The uni-directional air flow cabinet is run and particulate counts are taken. The inoculation machines are cleaned using 0.1M NaOH, WFI quality water and isopropyl alcohol. The machine is sanitized afterwards using 0.1M NaOH. After sanitization, a 120 L bag of prepared inoculum is attached, the machine is primed and a delivery check is performed.

Egg trolleys are moved through the egg receipt area as described in section 2.2. The trolleys are aligned with an automatic tray de-stacker. Trays are removed from the trolleys and conveyed into one of two EB132 inoculation machines under a laminar flow environment. Trays are moved into position and then injected in 3 stages: each egg is pierced, injected with inoculum, each needle is sanitized after every injection with 0.1M NaOH. 0.18 – 0.22 mL of prepared inoculum is injected into the allantoic cavity of each egg. The injection heads then lift and the trays of inoculated eggs are conveyed and automatically transferred back onto a trolley using an automated tray stacker. The trolleys of inoculated eggs are then transferred to waiting incubators using self-guided vehicles (SGVs).

2.4 Secondary Incubation

The goal of this step is promote virus growth and replication by providing incubation at the proper environmental conditions. Virus replication is stopped and eggs are prepared for allantoic fluid harvest via chilling.

2.4.1 Incubation

After inoculation, eggs racks on trolleys are transported and loaded into incubators in a specific load pattern by SGVs. The temperature and humidity of the incubators used are pre-set according to each strain before the incubators are loaded. The incubators are set at 34 ± 2ºC (the temperature setpoint varies per strain and is set ±1ºC tolerance) and 65 ± 10% RH. The eggs will be incubated for 48 – 72

hours. Each incubator holds up to 44 trolleys. The incubation time starts when the last egg trolley enters the incubator and the incubator door closes.

The ceilings, walls and floor are cleaned and the cooling coils are disinfected between each incubation process, per procedure.

2.4.2 Egg Chilling

After incubation the trolleys of eggs are removed from the incubators, transported and loaded into blast chillers in a specific load pattern via SGV. Each blast chiller holds up to 22 trolleys.

The temperature of the eggs is 34 ± 2ºC while in the incubators, after transfer to the blast chillers the temperature is reduced to a range of 2 ± 2ºC over a period of 4 hours. The eggs are kept below 4ºC for a minimum of 4 hours per United Kingdom Home Office Application: Animals (Scientific Procedures) Act 1986. Upon completion of chilling the trolleys are removed to the harvest area one at a time.

The blast chillers are regularly cleaned and sanitized per procedure as part of UM cleaning.

2.5 Harvest

The purpose of this step is to recover the virus containing allantoic fluid from the eggs.

2.5.1 Allantoic Fluid Harvesting

The harvesting trains are comprised of a tray destacker, conveyor, cutter, inspection conveyor and fluid harvester in two sections, "A" and "B." The fluid harvester is connected to a fixed processing vessel and skid. Both harvesting lines are located under a uni-directional air flow area within the harvest room in Site 4.

There are two harvesting trains currently used in the harvest area.

The harvesting machines are cleaned and prepared prior to start of harvest. The destacker, conveyor, egg cutter and inspection conveyor are cleaned and wiped down by hand. The fluid harvester is disassembled – the machine surfaces are cleaned by hand while the harvest probes are cleaned out of place in the equipment wash room. The harvest probes and disposable tubing are sanitized using an autoclave prior to installation for use. The harvest vessel skids and transfer lines are cleaned in place using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. Some vessel peripherals (hoses, filter housings, etc.) are removed and cleaned out of place in the equipment wash room. The vessel is reassembled with filters and hoses and sanitized in place using clean steam.

Egg trolleys are removed from the blast chillers and aligned in front of the destackers one at a time. Egg trays are removed from the trolleys and conveyed to a cutter where the eggs are raised so that the tops of the eggs show slightly through sized holes in a stainless panel. A knife edge cuts the top off each egg and vacuums the waste shell to a waste container. The eggs are then conveyed to a visual inspection station where operators remove any unsuitable eggs. Eggs removed from the inspection station are counted and sent to the waste system.

Egg trays are transported to the fluid harvesting machine. Stainless steel harvest probes are lowered into the allantoic fluid of each egg at pre-set X- and Y- axis locations and height. The allantoic fluid is collected by vacuum cycle (vacuum pulse at pre-set vacuum and time duration, pause for pre-set duration, vacuum pulse at pre-set vacuum and time duration) into the harvest vessel. Approximately 8-10 mL of allantoic fluid is harvested per egg. Once the vacuum cycle has completed, the trays of eggs minus the harvested allantoic fluid are advanced. The trays are conveyed to a tray tipper and macerator for disposal of solids waste. The used trays are run through a tray washer, cleaned using CIP 100 and purified water and returned to the egg receipt area. Used trolleys are washed in a pass-through washer using CIP 100 and purified water and returned to the inoculation area.

Each time an egg tray advances past the "A" section of the fluid harvester a signal is sent from the fluid harvesting machine to a peristaltic pump which adds 1.2 M Sodium Citrate to the harvest vessel to

minimize virus aggregation and adsorption to egg yolk components (yolk proteins, lipids, etc.) in order to maximize yield. A target of 23 mL of sodium citrate is added for each tray that passes.

Allantoic fluid is continuously transferred to the harvest vessel. The vessel is temperature controlled between 4 - 15ºC, (temperature target 11ºC) via recirculation of cooling water. Each time the level of allantoic fluid in the harvest vessel reaches a pre-determined set point, the fluid is pumped through an overhead transfer line via diaphragm pump to the bulk AF vessel in the inactivation area.

2.5.2 PBS Buffer Chase

Once all the egg trolleys have been harvested, approximately 45 L of PBS buffer pH 8.0 is transferred into each harvest vessel using the same peristaltic pump as the Sodium Citrate addition. This PBS buffer is then used to chase any held volume of allantoic fluid in the vessel / transfer lines into the bulk AF vessel in order to maximize yield. PBS pH 8.0 has been selected as a chase fluid to provide buffering capacity at optimum pH for formaldehyde inactivation.

2.6 Clarification

The purpose of this step is to remove solids waste from the harvested allantoic fluid via continuous centrifugation.

2.6.1 Bulk AF Vessel

The bulk AF vessel is a 1400 L stainless steel vessel used as a break tank for allantoic fluid. Prior to production, the bulk AF vessel is cleaned in place using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. The vessel is assembled with a steam-through connector attached to a 200 L bag / pallet tank containing 120 L of PBS buffer pH 8.0 and sanitized in place with the harvest transfer lines using clean steam.

During production allantoic fluid is transferred into the bulk AF vessel from the harvest vessels on both harvest trains. The fluid in the vessel is temperature controlled to 4 - 15ºC by recirculation of cooling water within the vessel jacket and agitation via bottom mounted magnetic mixer. The volume of the fluid is allowed to increase until a sufficient amount of fluid has accumulated so that the rate of continuous centrifugation will not empty the vessel and cause the centrifuge to hold in its processing phase.

Once all the egg trolleys have been harvested and the chase from the harvest vessels has been performed, 120 L of PBS buffer pH 8.0 is transferred into the empty bulk AF vessel using a peristaltic pump. This PBS buffer is then used to chase any held volume of allantoic fluid in the vessel / transfer line into the centrifuge, through the pre-filters and into the UF concentration vessel in order to maximize yield.

2.6.2 Centrifugation

The clarification centrifuge is a Westfalia CSC-20 disk stack centrifuge. Prior to production, the centrifuge is cleaned in place using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. The centrifuge is sanitized in place with the transfer line coming from the bulk AF vessel using clean steam.

Once the level of allantoic fluid has risen sufficiently in the bulk AF vessel, a centrifugal pump transfers the fluid to the inlet of the clarification centrifuge at constant pressure. The centrifuge separates solids waste from the process stream based on density using centrifugal force generated by rotational speed. The base and hood of the centrifuge are jacketed to provide heat removal via recirculation of cooling water – the jacket provides heat removal only, not temperature control. Solids are captured within the void space inside the bowl and discharged at regular intervals into the waste stream. The clarified process fluid is pumped up and through the discharge line and transferred overhead to the pre-filters.

Note: The centrifuge used in Liverpool is a larger scale model of the unit which is used in Siena. Technical studies will be performed to establish equivalent operating parameters for Aflunov processing.

Once parameters have been established, this document will be revised to add the processing parameters that are specific to Liverpool equipment.

2.6.3 Pre-filtration

The pre-filters are a series of four 20" x 8.0 µm filters used to protect the UF membranes from large solids break-through from the clarification centrifuge. Prior to production, the pre-filters are cleaned in place with filter "dummies" using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. The filters are installed afterwards and the skid and filters are sanitized in place with the transfer line coming from the clarification centrifuge using clean steam.

During processing, clarified allantoic fluid from the centrifuge flows through the four pre-filters in parallel. Fluid flows at the same flow rate as processed through the centrifuge. Typical differential pressure is anticipated to be 0 – 2 bar. The valves around the filters are configured to minimize air trapped in the housings and maximize filtration area by bleeding air through the tops of the housings whenever air is detected. The air bleed closes as soon as no air is detected. The air bleed function operates independently on each filter housing. Once the allantoic fluid has passed through the pre-filters it flows into the concentration vessel of the Ultrafiltration skid.

2.7 Concentration and Inactivation

The purpose of this step is to concentrate the clarified allantoic fluid and inactivate the influenza virus.

2.7.1 Concentration

The upstream ultrafiltration skid is a system consisting of a 1200 L vessel, a rotary lobe pump and a series of piping and valves to hold 120 x 300 kDa ultrafiltration membrane cassettes. Prior to production, the skid and membranes are cleaned in place using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. The UF membranes are then stored in 0.1 M NaOH, while the piping module is sanitized in place using clean steam. The storage solution is flushed out using PW prior to production.

During processing, allantoic fluid is allowed to accumulate within the concentration vessel until it reaches a volume of 900 L. Temperature of the vessel is controlled to 8 - 15ºC via recirculation of cooling water within a vessel jacket. Once the fluid rises to the required level, the pump circulates the fluid within the system at a pressure of 1 bar. The allantoic fluid flows tangentially across the membranes. As the fluid flows across the membranes, a fraction of fluid containing particles smaller than 300 kDa pass through the membrane to the permeate waste line and into drain while fluid containing particles larger than 300 kDa (including virus) are returned to the concentration vessel via retentate flow path.

The pump stops circulating fluid once the vessel level has decreased to 800 L. The ultrafiltration skid runs this concentration step continuously between the start and stop concentration set points until all harvest and clarification operations have completed. The final volume of concentrated allantoic fluid is 800 L. Once concentration has completed, the ultrafiltration membranes are flushed with purified water to maximize yield. The final collected, concentrated allantoic fluid has a pH range of 7.5 – 8.5 and volume of 900 L.

2.7.2 Inactivation

There are two 1600 L vessels utilized for inactivation in site 4: inactivation vessel A and inactivation vessel B. The vessels are used alternately for batch inactivation of concentrated allantoic fluid.

Each of these vessels is temperature controlled using recirculated water and a temperature control unit (TCU). Both vessels also utilize a bottom-mounted, magnetically driven agitator. Prior to production,

the vessel which will be utilized is cleaned in place using a remote CIP skid with 1.0 M NaOH, 0.2 M H_3PO_4 and purified water. The receiving vessel and UF transfer line are sanitized in place using clean steam.

Once the concentrated allantoic fluid has been collected, 0.5 mL of 40% aqueous solution of formaldehyde per L of allantoic fluid is measured out under a chemical fume hood. The formaldehyde is transferred into a glass plasma bottle and closed with a cap that includes a sterile vent filter and dip tube. The formaldehyde is placed in a bottle holder and connected to a dip tube on the concentration vessel via tubing and a steam-through connector. The entire contents of the plasma bottle are transferred into the concentration vessel via peristaltic pump.

Once transferred, the agitator within the concentration vessel rotates at high speed while the solution is recirculated within the tank via a by-pass line to mix the solution and ensure formaldehyde contact with all concentrated AF. This mixing takes place for a minimum of 30 minutes. While the allantoic fluid and formaldehyde solution are mixing, an inactivation vessel is pre-heated. Once the jacket return temperature reaches setpoint, the allantoic fluid is transferred overhead into the preheated inactivation vessel through a dip tube. At the end of the transfer the line is blown down with clean compressed air.

After transfer, the allantoic fluid is heated and mixed continuously. The inactivation step is timed once the allantoic fluid temperature reaches 20ºC. The fluid is held between 20 - 30ºC and mixed continuously at low speed for 18 - 24 hours, depending on strain.

Once the inactivation step has completed, the inactivated allantoic fluid is transferred to one of two inactivated bulk fluid vessels (IBF vessels) in the downstream area via a clean, sanitized transfer line utilizing pressure transfer.

Note: The ultrafiltration vessel used for formaldehyde mixing in Liverpool has different volume and dimensions than the ultrafiltration and inactivation vessels which are used in Siena. Technical studies will be performed to establish equivalent formaldehyde mixing parameters for Aflunov processing. Once parameters have been established, this document will be revised to add the processing parameters that are specific to Liverpool equipment.

2.8 Area Classification

Novartis V&D has classified the egg receipt and exterior corridors of the Site 4 upstream manufacturing area as clean, unclassified. All other areas within the Site 4 upstream manufacturing area (inoculum prep, inoculation, post-incubation, harvest and inactivation) are classified as Novartis "Zone 2."

Conclusions

There are no conclusions associated with this document.

Recommendations

There are no recommendations associated with this document.

ATTACHMENTS

Attachment No.	Documents/Contents	Ref. Section	No. of Pages
1	Process Description Chart: Agrippal Platform and Derivative Products	2	12
2	Process Flow Diagram: Agrippal Platform and Derivative Products	2	6

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.1.1	Egg Delivery. Deliver pre-incubated fertile hens eggs to from accredited suppliers to Novartis manufacturing facilities.	Egg trays Trolleys	Hens eggs	Hens eggs	PIU	Transportation Temperature = 12 - 18ºC Transportation Humidity > 50% Cold Storage temperature = 12 - 18ºC Cold Storage Humidity > 50%	Maximum cold storage = 7 days	Temperature Humidity	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.1.2	Egg wash. Wash exterior of eggs using chlorine based cleaner prior to primary incubation phase. Eggs make 2 cleaning passes in egg wash machine.	MS Technologies egg washer machines Egg trays Trolleys	Hens eggs 500g Chlorowash tablet per MST machine QUAT 800 (quaternary ammonia based cleaner)	Washed hens eggs	PIU	Chlor-wash > 200 ppm Cl^- T = 44 ± 3ºC Chlor-wash > 200 ppm Cl^- T = 48 ± 3ºC QUAT 800 > 300 ppm QAC	Air dry = min 2 hours	$[Cl^-]$, Temperature [QUAT], Temperature Time to air dry	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.1.3	Primary incubation. Incubationof fertile hens eggs prior to inoculation.	Incubators Egg trays Trolleys	Washed hens eggs	Pre-incubated hens eggs	PIU	Temperature = 37.0ºC ± 1.0ºC Humidity = 45-65% RH	10 - 12 days	Temperature Humidity Time	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.1.4	Candling. Inspection of fertile hens eggs prior to inoculation. Removal of infertile, moribund and non-viable eggs.	Embrex automatic candling machine (light transmission) Manual candling booth Candling light wand	Pre-incubated hens eggs	Candled, pre-incubated hens eggs	PIU	Ambient	Rate: 8 trolleys per hour	N/A	N/A	Non-viable eggs removed and replaced

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.1.5	Warm room storage. Hold eggs at temperature while awaiting transport to site 4.	Warm room Egg trays Trolleys	Pre-incubated hens eggs	Pre-incubated hens eggs	PIU	Set point = 33ºC Range = 28-38ºC	Max = 4 hours	Temperature Time	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.2.1	Egg Receipt. Transport and receive pre-incubated fertile hens eggs from Novartis PIU to Site 4 primary manufacturing facility.	Egg trays Trolleys	Washed, pre-incubated hens eggs	Washed, pre-incubated hens eggs	R311 / 05 R311 / 06 R311 / 20 R311 / 21	Ambient	Max 1 hour hold	Time	N/A	Eggs damaged during transport rejected and returned to PIU.

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.2.2	Candling. A minimum of 5.2% of the eggs received are manually candled to check quality of the eggs.	Manual candling booth Fiber optic candling light assembly Egg trays Trolleys	Washed, pre-incubated hens eggs	Inspected hens eggs	R311 / 07	Ambient Dark room	N/A	Visual inspection	N/A	Non-viable, damaged eggs removed and replaced.

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.3.1	Inoculum Preparation. Prepare virus seed dilution for use in egg inoculation machines.	Laminar flow cabinet Pallet tank Peristaltic pump Pipettes Nunc tubes Nalgene bottles	0.5 mL vials virus seed 120 L bag PBS buffer pH 8.0 1L bottle antibiotic solution	120 L bag inoculum	R311 / 02	Laminar flow, aseptic technique	Re-circulate for mixing 10 minutes	Infectivity	Sterility Env. Monitoring	Dilution of strain used for production

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.3.2	Inoculation. Inoculate prepared flu virus into the allantoic cavity of the embryonated eggs.	Embrex B132 inoculation machines Clean Site 4 trolleys Self guided vehicles Egg trays Trolleys	Hens eggs 120 L prepared inoculum solution 0.1 M NaOH	Inoculated hens eggs	R311 / 05 R311 / 01	Inoc. Volume = 0.18 - 0.22 mL / egg Infectivity > 10^5 EID 50/mL	N/A	Inoculation volume	Particulate checks QC plate checks Visual inspection: sanitant ring, needles (every 4 trolleys) Infectivity	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.4.1	Virus Incubation. Allow virus growth by incubation.	Besthatch BH V54 Incubators (IC-312-001 – 008) Egg trolleys Egg trays	Inoculated hens eggs	Incubated hens eggs	R312 / 01	Incubation temperature = 34ºC ± 2ºC (strain dependant) Humidity = 65 ± 10% RH	48 - 72 hrs	Temperature Humidity	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.4.2	Egg chilling. Chill the eggs at the end of the incubation in order to stop virus replication, terminate the chicken embryo and allow subsequent allantoic fluid harvesting.	Blast chillers (CH-313-001 – 004) Egg trolleys Egg trays	Incubated hens eggs	Chilled hens eggs	R312 / 09	Egg chilling temperature (taken from warmest point) < 4ºC	12 hrs (minimum 4 hours after egg temperature < 4ºC)	Egg Temp Time	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.5.1	AF Harvest. Recover the virus containing allantoic fluid from eggs.	Egg trays Egg trolleys Destackers Egg cutters Inspection conveyor Powell Bros. fluid harvesting machines (EH-314-027, 028, 037, 038)	Chilled hens eggs 1.2 M Sodium citrate	Harvested allantoic fluid Solid egg waste Used egg trays	R314 / 01	Harvest Vessel ~~temperature~~ = 4 - 15ºC	Target: 10 – ~~14 hours~~	Percentage discarded eggs Harvest probe positions Vacuum / time; pause time; vacuum / time	N/A	Maximum egg rejection ~~percentage~~ <10%

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.5.2	PBS buffer chase. Maximize recovery of allantoic fluid.	Harvest vessels (VL-314-001, 002) Peristaltic pumps	Harvested allantoic fluid PBS buffer pH 8.0	Harvested allantoic fluid	R314 / 01	ambient	Target: 30 minutes	Pump speed	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.6.1	Bulk AF. Hold allantoic fluid at controlled temperature and provide constant supply of fluid to clarification centrifuge.	Bulk AF vessel (VL-315-001) Peristaltic pump	Harvested allantoic fluid	Harvested allantoic fluid	R315 / 01	Temperature = 2 - 8ºC	Target duration = 14 – 16 hours	Temperature Agitator speed	Haemag-glutination	N/A

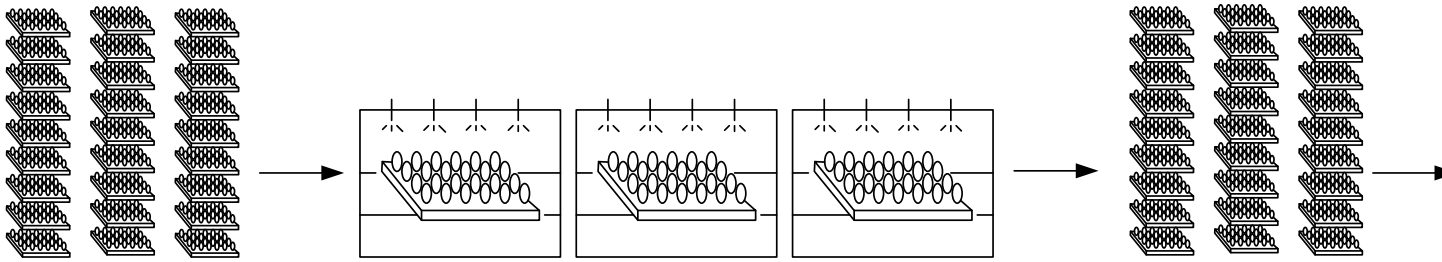
Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.6.2	Centrifugation. Solids waste removal from harvested AF via continuous centrifugation.	Centrifugal feed pump (PS-315-003) Westfalia CSC-20 disk stack centrifuge (CG-315-011)	Harvested allantoic fluid	Clarified allantoic fluid Solids waste	R315 / 01	Feed pressure = TBD Flow rate = TBD Bowl speed = TBD Ejection frequency = TBD Temperature = TBD	Target duration = 10 – 12 hours	Feed pressure Flow rate Bowl speed Ejection frequency Temperature	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.6.3	Pre-filtration. Protect UF membranes from large solids break through.	Pre-filtration skid (ZZ-315-001) 4 x 8.0 µm filters (AB2DC7P)	Clarified allantoic fluid	Clarified allantoic fluid	R315 / 01	Flow rate = TBD Differential Pressure = 0 – 2 bar	Target duration = 10-12 hours	Flow rate Differential Pressure	N/A	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes

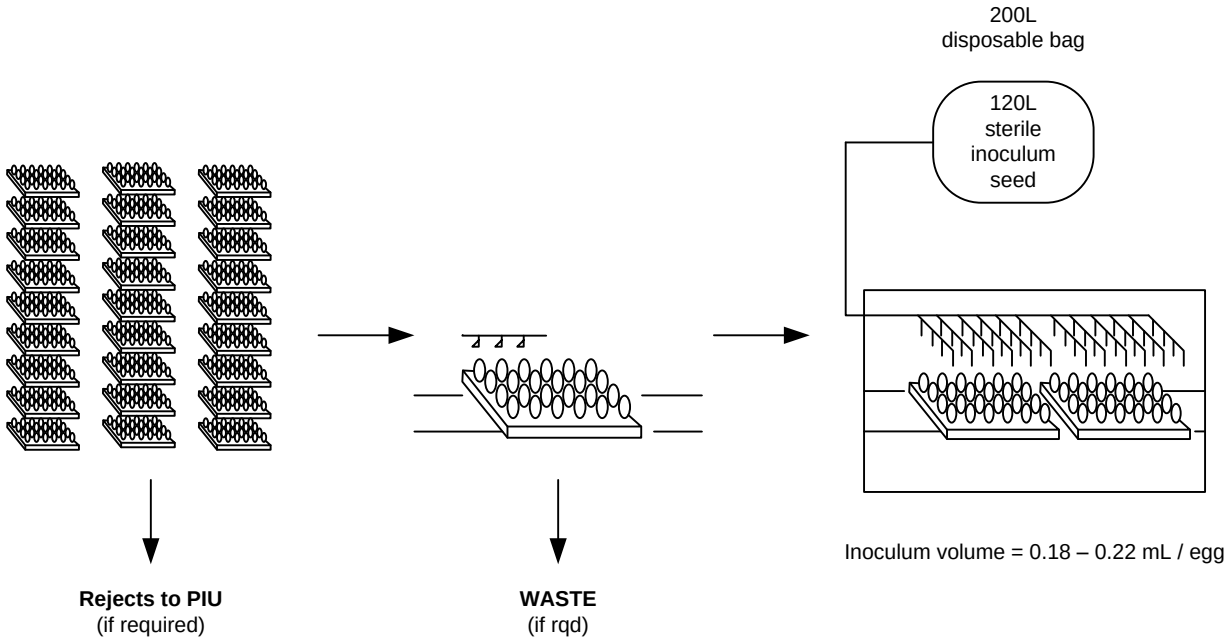
Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.7.1	Concentration. Concentration of allantoic fluid prior to inactivation.	Ultrafiltration Vessel (VL-315-031) 300 kDa UF membranes	Clarified allantoic fluid	Concen-trated allantoic fluid	R315 / 01	Temperature = 8.0 – 15.0ºC Pressure = 1 bar Final concentrated volume = 900 L Final pH range = 7.5 – 8.5	Target duration = 10 – 12 hours	Membrane area Membrane pore size Flow rate (permeate, retentate) Pressure (permeate, retentate) Volume Temperature	<u>Pre-concentration</u> Hemag-glutination <u>Post-concentration</u> Hemag-glutination Bioburden Endotoxin	N/A

Step #	Step Description and Objective	Equipment	Inlet Streams	Exit Streams	Room #	Process Conditions	Duration	Control Parameters	Analytical Tests	Decisions / Outcomes
2.7.2	Inactivation. Inactivation of live virus using 40% formaldehyde.	Chemical fume hood Plasma bottle / cap Peristaltic pump Ultrafiltration vessel / agitator (VL-315-031) Inactivation vessel A / agitator / TCU (VL-315-041)	Concen-trated allantoic fluid 40% formal-dehyde	Inactivated bulk fluid	R315 / 01	Temperature = 25 ± 1.0ºC	Minimum inactivation duration = 24 hours (strain dependant)	Volume CHOH Pump speed Transfer pressure Agitator speed (UF and inactivation) Inactivation temperature	Haemag-glutinaton Bioburden	Inactivation parameters determined for each strain via lab scale studies, then confirmed at large scale for each manufac-turing campaign.

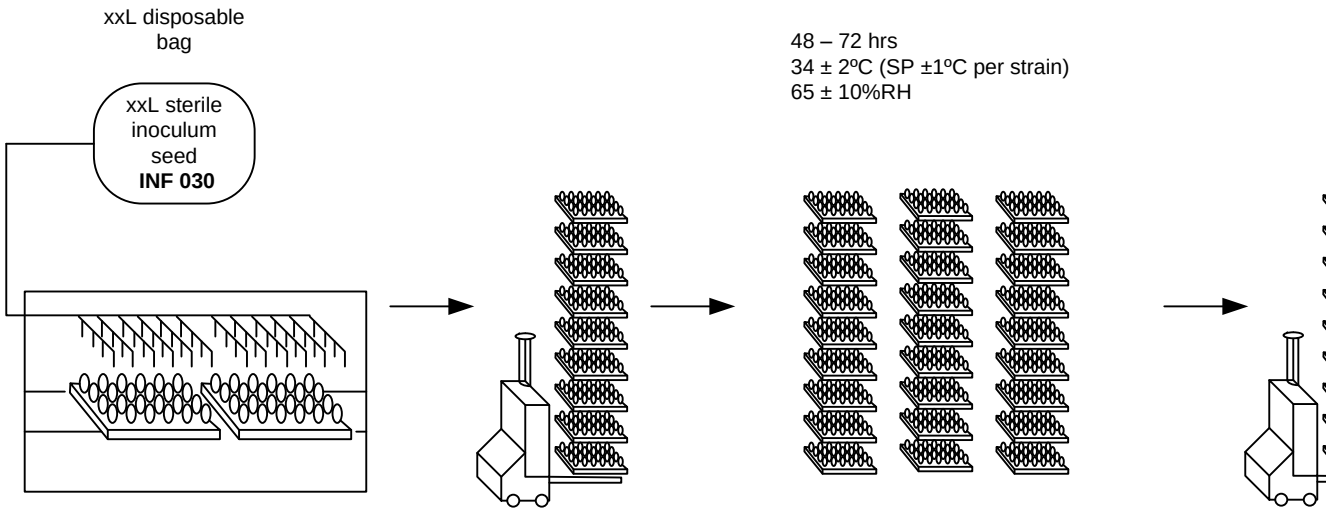


Note: Air dry at room temperature for minimum 2 hours.

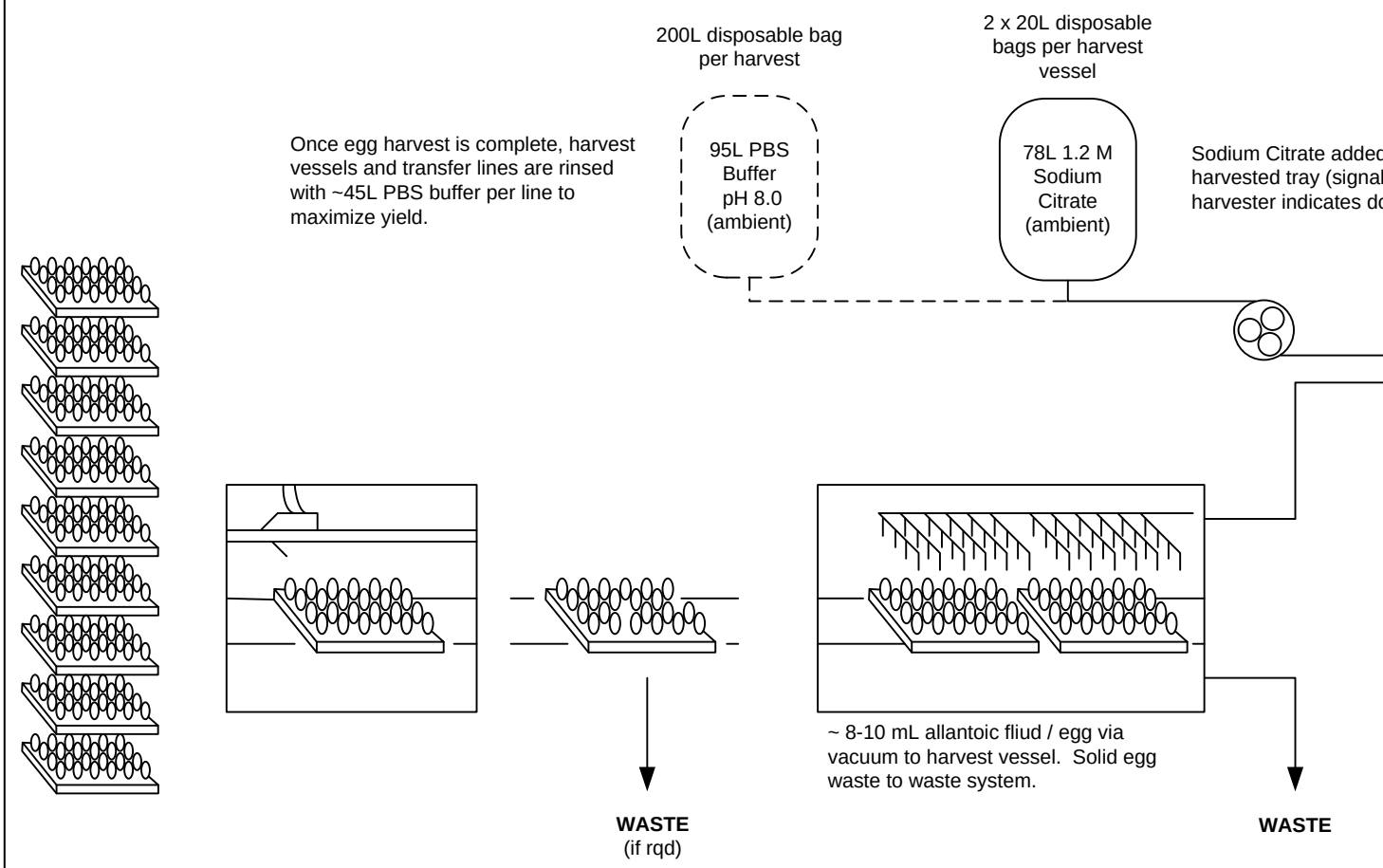
Process Flow: PIU Operations, (steps 2.1.1 through 2.1.5)



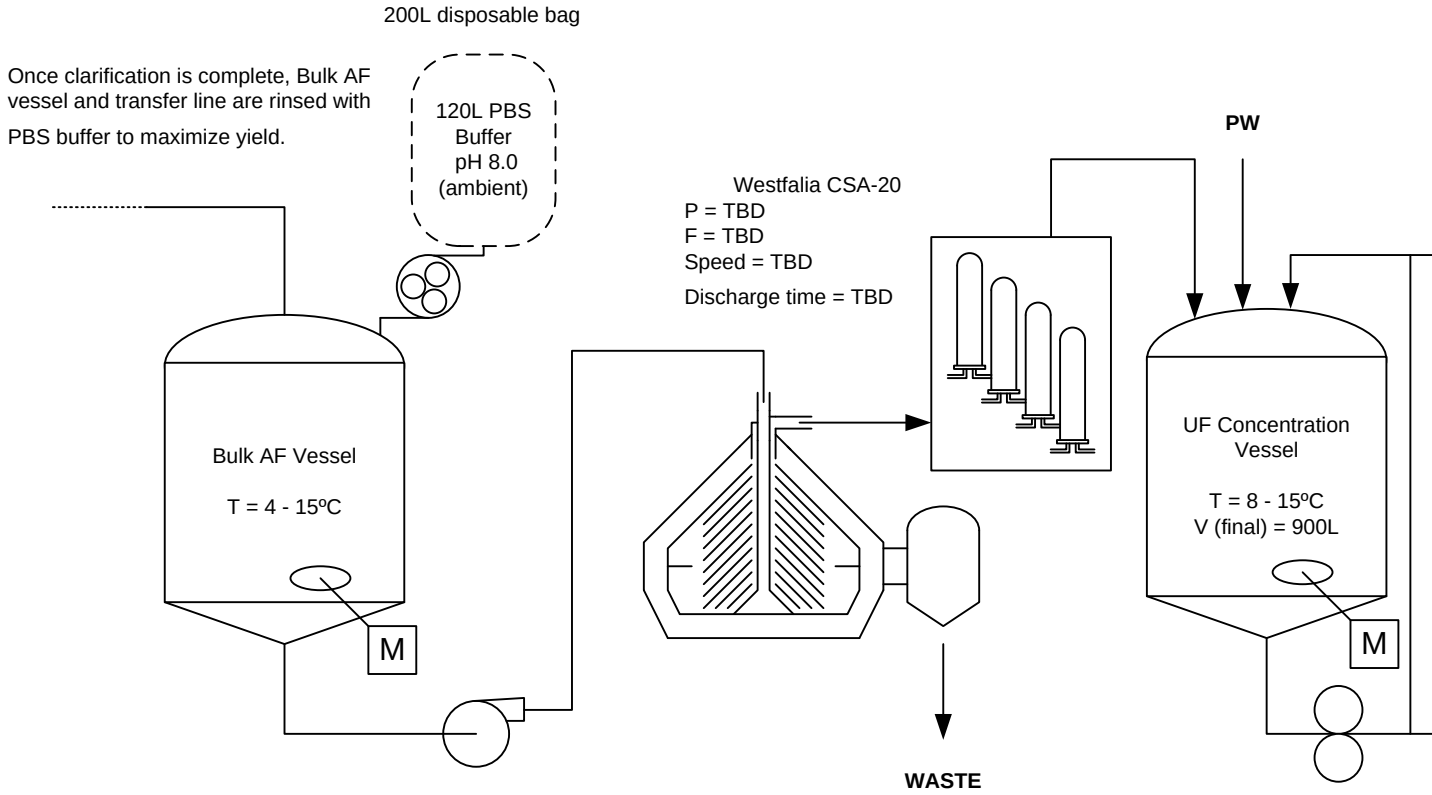
Process Flow: Site 4 Egg Receipt through Inoculation, (steps 2.2.1, 2.2.2 and 2.3.2)



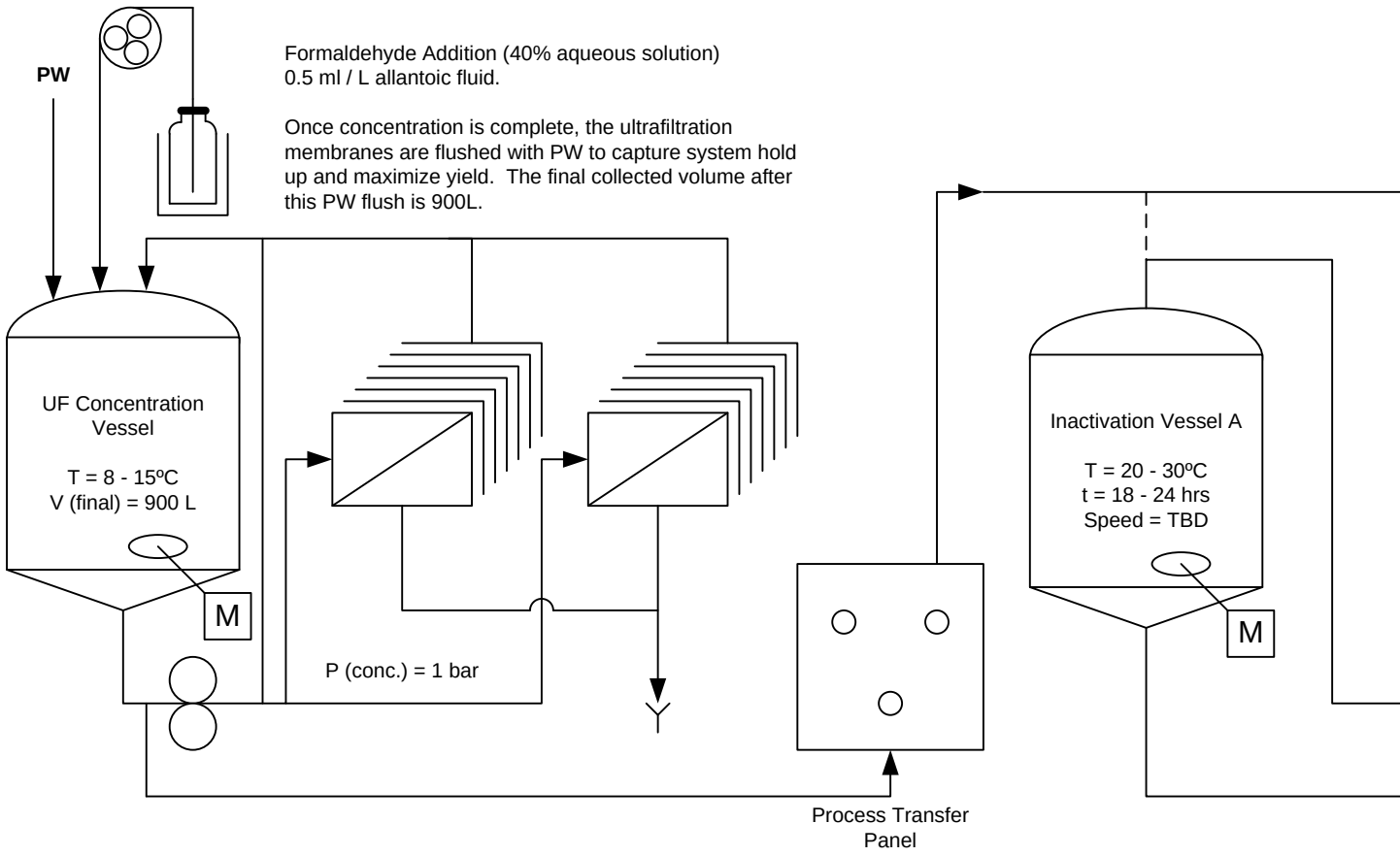
Process Flow: Secondary Incubation and Chilling, (steps 2.4.1 through 2.4.2)



Process Flow: Harvest, (steps 2.5.1 through 2.5.2)



Process Flow: Clarification, (steps 2.6.1 through 2.6.3)



Process Flow: Concentration and Inactivation, (steps 2.7.1 through 2.7.2)