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Quantifying Responsiveness in the Vaccine Industry to Evaluate and Improve Pandemic Response

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by

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Abstract

Title: Quantifying Responsiveness in the Vaccine Industry to Evaluate and Improve Pandemic Response

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In the wake of the pandemic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) we can look at many aspects of the global response, including social, scientific, and governmental. Current research in the areas of vaccine development and manufacturing find the process of developing a new vaccine takes an especially long time and is unresponsive. Understanding the factors that influence responsiveness can help organizations be better prepared to address the needs of society should another pandemic strike. Responsiveness can be linked to product, process, and volume. The vaccine development and manufacturing process historically takes years to reach distribution for public use. In the face of potential pandemics, learning from SARS-CoV-2 vaccine responsiveness will provide essential information for future decision making. This paper will propose a method to quantify and evaluate the responsiveness of manufacturing processes and vaccine development within the vaccine industry by considering various elements of an organization's vaccine development and supply chain process. We created a model to evaluate characteristics within the supply chain for vaccine delivery. The model can be used to better understand an organization's strengths and weaknesses in their supply chain. In turn, an organization can be better prepared to act swiftly against a future pandemic.

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Dedication

I would like to dedicate the writing of this thesis to the following people.

First, I would like to dedicate this thesis to my parents. I appreciate all your love and support and always pushing me to be my best.

Next, I would like to dedicate this thesis to my brother for always being there for me whenever I need it.

Lastly, I would like to thank all the members of the vaccine industry that helped with the creation of SARS-CoV-2 vaccines. Your hard work and dedication to this task have saved many lives.

Chapter 1
Introduction

Motivation

Ebrahim et al. describe that in many industries, fast-paced development and customer driven market creates substantial competition within manufacturing companies. Researchers have studied the vaccine industry and found that it has historically been unresponsive and slow to develop products compared to other industries (Moalla, Bouras, & Neubert, 2007) (Rosa, Prazeres, Azevedo, & Marques, 2021). The recent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic shows that there is a need for a fast paced, rapid response development process to quickly respond to global health concerns. There are many lights in which people can evaluate how the world and the vaccine industry handled the SARS-CoV-2 pandemic such as politically, scientifically, and socially. Despite all these potential lights, the motivation and scope of this thesis is to evaluate the responsiveness of the development, manufacturing, and supply chain in the vaccine industry to see what areas need to be focused on to develop a rapid response supply chain.

Objectives

Though it is unfortunate that the SARS-CoV-2 pandemic has been so devastating throughout the world there is an opportunity to evaluate the vaccine industry's responsiveness. The following main objectives need to be met to be able to evaluate the responsiveness of the vaccine industry:

1. Determine what factors affect a vaccine company's ability to be responsive in developing a vaccine to meet an unexpected high demand within a desired customer wait time.
2. Use these factors to develop an evaluation model to quantify a company's performance in terms of responsiveness.

The evaluation model will be used to evaluate several areas in the response of three different SARS-CoV-2 supply chains. These supply chains include, BioNTech had they developed a vaccine on their own, the Pfizer and BioNTech partnership to develop a vaccine, and the Johnson and Johnson vaccine. These supply chains were selected to evaluate some specific areas of the vaccine industry. These areas include:

1. How the type of vaccine technology can affect the responsiveness of the vaccine supply chain.
2. How intercompany partnerships can affect the responsiveness of the vaccine supply chain.

There are several other vaccine companies that exist that have developed SARS-CoV-2 vaccines such as the Moderna. Despite there being other vaccine supply chains, this thesis will focus exclusively on the BioNTech, Pfizer, and Johnson and Johnson vaccines and supply chains because of these analysis objectives. The methodology and analysis used in this thesis can be used to evaluate the other vaccine supply chain responsibilities as well.

Responsiveness of Manufacturing

Any physical goods that a company or organization deems that a customers will want will eventually need to be manufactured. The manufacturing process for various goods can be vastly different and can involve specific steps that needs to be accounted for when developing that process. Some of the many things that will need to be considered when developing a process includes, technologies involved, quality control, upstream supply chains and downstream supply chains. These factors can be quite difficult to consider for the product that is being manufactured and can get even more complicated when the customer demand of the specific product will not remain constant. This is when considering the responsiveness of manufacturing can help a company better develop a manufacturing process for an everchanging customer demand. Responsiveness in terms of manufacturing has been described as, “the ability of manufacturing company to respond quickly [to] customer demands and market changes” (Ebrahim, Ahmad, & Muhamad,

2014). There are many things that can be considered when trying to evaluate the responsiveness capabilities of a company, industry, or manufacturing process.

Vaccine Development and Manufacturing

Vaccine Development

The birth of immunology occurred in the late 18th century when scientists started researching ways to protect people from smallpox. Since then, the creation and deployment of vaccines within a population has saved many lives from diseases such as Polio, Smallpox, Pertussis, Measles and more. As time has progressed so has our understanding of how vaccines and diseases work which as improved our methods of researching and manufacturing vaccines. There are several types of vaccines that exist such as live-attenuated vaccines, inactivated vaccines, protein subunit vaccines, toxoid vaccines, viral vector vaccines, and mRNA vaccines. Each of these vaccine types go about creating an immune response in very different ways and a company must choose which one to use based on various factors such as disease pathology, desired immune response, and manufacturing techniques.

Vaccines play an important role in the response to epidemics and pandemics which is why the development of vaccines during a pandemic is important. An example of vaccines being developed in response to an epidemic include the response to the influenza A (H1N1) pandemic in 2009. In April 2009 the World Health Organization (WHO) declared the H1N1 flu outbreak a pandemic, and in September there were approved vaccines to help fight that pandemic. By August 2010 the WHO was able to declare the end of the H1N1 pandemic due to the assistance of vaccines (Centers for Disease Control and Prevenstion, National Center for Immunization and Respiratory Diseases, 2019). More recently the pandemic of the SARS-CoV-2 virus has brought the vaccine development process back into the spotlight in many areas of the world. There are some pathological differences between the SARS-CoV-2 virus and the H1N1 influenza virus that make fighting them different, but this shows the development of the vaccines is an important tool in fighting pandemics and health crisis.

Vaccine Manufacturing

Manufacturing of vaccines are different than that of the manufacturing of other goods such as the newest cell phone or children's toy. Lemmens et al. look at some of the key issues of the vaccine supply chain and explain how some of the differences of vaccine manufacturing and how it is different from other goods (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). They explain that the active ingredient to vaccines is an antigen molecule that will help a person's immune system create antibodies for a given disease without having been exposed to the disease. There are several techniques that exist for creating this desired effect in the immune system including utilizing an inactive portion of the disease, to utilizing cellular processes to create the antigens, and many more. All these techniques require some sort of chemical and biological manufacturing to produce. When these manufacturing processes are scaled up to produce bulk vaccines it can create some variability in the product. This variability in product, means that that manufacturing processes are highly regulated by regulation agencies and employ quality control measures. Overall, the manufacturing process for a specific vaccine is going to determine on disease pathology, and the type of vaccine being produced. A description of the basic steps of manufacturing a vaccine will be discussed in the literature review.

Company Details

This thesis will focus on the responsiveness of two of the vaccines that were developed to fight the SARS-CoV-2 virus. The first is the Pfizer-BioNTech mRNA vaccine and the second is the Johnson and Johnson viral vector vaccine. The next sections will provide some background on each of the three companies. There are some other companies that have other vaccines, such as Moderna, who created an mRNA vaccine to combat the SARS-CoV-2 pandemic. Moderna could have been selected as a company to investigate responsiveness, but in terms of the specific analysis objectives being evaluated, it was determined that a full analysis of the company and supply chain was not necessary.

BioNTech

Biopharmaceutical New Technologies or BioNTech is a German pharmaceutical company based in Mainz, Germany. BioNTech was founded in 2008 as an individualized cancer treatment and medicine company and employs 1300 people. As a part of their vision of bringing individualized cancer treatment BioNTech has been investigating and researching mRNA-based therapies and vaccines. BioNTech has developed an expertise in mRNA development and is working with partners to develop vaccines for multiple diseases and oncology purposes. One of these development projects included a collaboration with Pfizer on an influenza mRNA vaccine. This initial collaboration led to Pfizer and BioNTech partnering to create a SARS-CoV-2 vaccine. Earnings reports for BioNTech from 2018 show that their revenue was 127.6 million euros. In 2021 BioNTech revenues rose to 18,976.7 million euros due to the SARS-CoV-2 vaccine. (BioNTech, 2018) (BioNTech, 2022) (BioNTech, n.d.)

Pfizer

Pfizer is a pharmaceutical company that was initially founded in 1849 that now produces many different drugs. Some of Pfizer's most profitable products are pharmaceuticals like Eliquis, which is a drug that blocks the activity of clotting factors in blood, Ibrance, a breast cancer treatment drug, and Prevnar 13, a vaccine for the prevention of invasive pneumococcal disease. Pfizer has a wide variety of products and has plenty of experience and resources to develop vaccines. Pfizer employs approximately 79,000 people worldwide and has many manufacturing facilities around the world. Pfizer's earnings in 2018 was $53.6 billion. In 2021, Pfizer reported earnings of $81.3 billion. (Pfizer, 2022) (Pfizer, 2022) (Pfizer, 2021)

Johnson and Johnson

Johnson and Johnson is a large company that operates in multiple product areas including consumer health products such as lotions, and mouthwash; medical technology including orthopedic devices and surgical instruments; and finally pharmaceuticals such as vaccines. Some of Johnson and Johnson's primary pharmaceutical products include Stelara, a

Crohn's disease treatment medication, and Erleada, a prostate cancer treatment drug. In 2018 Johnson and Johnson's total earnings was $81.6 billion with $40.7 billion of those earnings being from pharmaceutical sales. Johnson and Johnson's 2021 total earnings from all three of their product areas totaled $93.8 billion. Of that $93.8 billion Johnson and Johnson reports that $52.1 billion comes from their pharmaceutical sales. (Johnson and Johnson, 2022) (Johnson and Johnson, 2019)

SARS-CoV-2 Pandemic

SARS-CoV 2 Pandemic and Vaccine Development Timeline

The SARS-CoV 2 virus was first discovered in December 2019 in the Wuhan Hubei Providence, China. Global health organizations began to track the progression of the virus in the coming months. The World Health Organization (WHO) declared the beginning of a pandemic in March of 2020.

Not long after the WHO declared the SARS-CoV 2 virus a pandemic the United States and other countries began the process of developing vaccines. In May of 2020 the U.S. Department of Health & Human Services began a program called Operation Warp Speed, the goal of which was to try and develop and manufacture vaccines as quickly as possible. There were other similar programs around the world to try and create vaccines. By December of 2020 the United States Food and Drug Administration had issued Emergency Use Authorizations (EUA) for two vaccines for adults, the Pfizer-BioNTech COVID-19 vaccine, and the Moderna COVID-19 vaccine. Not long after, in February 2021 a third vaccine the Johnson and Johnson COVID-19 vaccine was given EUA. Figure 1 shows the timeline of the development of various SARS-CoV-2 vaccines.

It is interesting that the vaccine development and manufacturing process that usually takes several years, was able to be completed in less than a year for many companies developing them. There are lots of things that contribute to why these companies were able to respond so quickly to a customer and market demand and develop these vaccines so quickly despite many challenges in the vaccine development and manufacturing process. Looking at the

responsiveness of manufacturing and applying this to the development and manufacturing process of the SARS-CoV-2 will allow investigation into the vaccine supply chain so that companies can prepare for the next pandemic or unexpected change in demand by addressing some improvement areas.

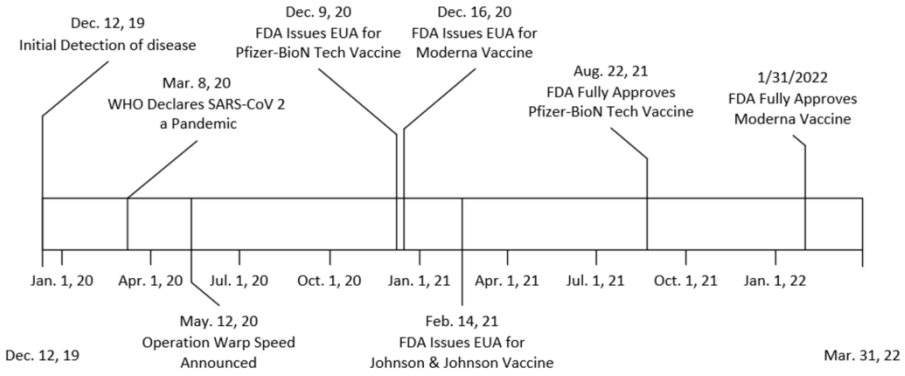

Figure 1 : SARS-CoV-2 Vaccine Development Timeline

SARS-CoV 2 Vaccines

In the United States, there are currently three vaccines in use that have been either approved or given emergency use authorization EUA by the FDA. These vaccines are produced by Pfizer-BioNTech, Moderna, and Johnson and Johnson. Two of these vaccines (Pfizer-BioNTech and Moderna) utilized an emerging vaccine technology called mRNA vaccines, and the other (Johnson and Johnson) utilize a more traditional vaccine technology called viral vector vaccines. These companies are being evaluated because much of the information about their vaccines are provided by the U.S. Food and Drug Administration and the Centers for Disease Control. Because of the availability of

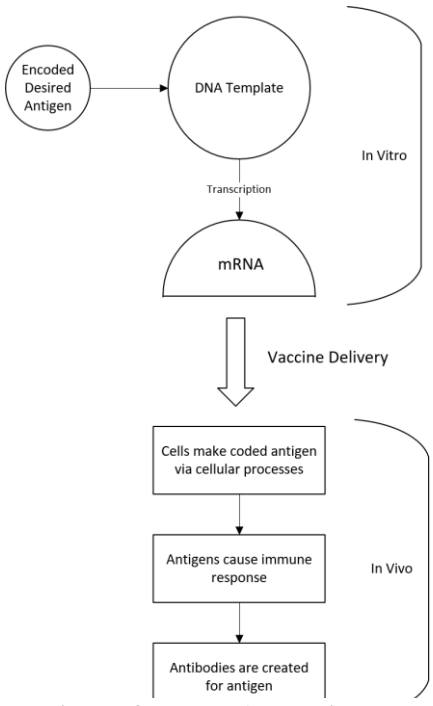

Figure 2 : mRNA Vaccine Process

information these companies will be looked at as opposed to other vaccines developed around the world.

The Pfizer-BioNTech and Moderna vaccines utilizes an emerging technology in pharmaceuticals called an mRNA vaccine. This vaccine utilizes messenger ribonucleic acid (mRNA) to utilize the cellular process of protein synthesis to create a protein that is an antigen that allows the immune system to create an antibody of a given disease. Rosa et al. describe the structure and delivery of an mRNA vaccine (Rosa, Prazeres, Azevedo, & Marques, 2021) (Centers for Disease Control and Prevention, 2021). First there must be a specific encoded antigen that they would like to have the body create. Next the researchers insert the encoded antigen into a DNA template that will code for the creation of the antigen within a cell. This template then undergoes transcription to turn it into mRNA. This mRNA is then created into a vaccine. When the vaccine is injected into the cytosol of the cell, the cell will use transcription to create the desired initial antigen. This antigen will then go on to create an immune response which creates the antibodies for a disease. This process is shown in Figure 2. Though the Pfizer-BioNTech and Moderna SARS-CoV 2 vaccines are some of the world's first vaccines that use this technology on a large vaccination scale they have been researched for many years (Centers for Disease Control and Prevention, 2022).

The Johnson and Johnson vaccine utilizes a more traditional viral vector vaccine technology to create a vaccine for SARS-CoV 2. This type of vaccine utilizes an inactive or modified version of the virus that is injected into the cytosol of the cells. The modified version of the virus then creates an immune response that creates the antibodies for the disease (Centers for Disease Control and Prevention, 2021).

The manufacturing and development of each of these vaccines is quite different and there are some pros and cons to each of the technologies. For example, viral vector vaccines can have a long development time because of the need to create a safe, inactive version or part of a virus that can produce the desired immune response (Rosa, Prazeres, Azevedo, & Marques, 2021). mRNA vaccines can have a quicker development time because the

developers just need to know how to encode for a specific antigen on the virus so they can make the vaccine (Rosa, Prazeres, Azevedo, & Marques, 2021). Companies like Pfizer-BioNTech and Moderna that have developed the mRNA vaccines for this pandemic have shown regulatory agencies the efficacy of their products to get full FDA approval. Despite this full approval the scientific and medical communities are continuing to evaluate various quality, safety, and efficacy of mRNA vaccines (Rosa, Prazeres, Azevedo, & Marques, 2021). These pros and cons can affect a pharmaceutical company ability to respond to changes in demand such as that of a pandemic.

Responsiveness in the Vaccine and Pharmaceutical Industry

There are several reasons why the vaccine industry needs to be concerned about responsiveness. The first reason is a utilitarian ethical reason in that vaccines are and have been a vital part of humanities plan to protect populations from various diseases. If research can evaluate the responsiveness of the vaccine industry, then it is possible to find ways to streamline the development and manufacturing process so that when potentially deadly diseases are discovered companies can respond quicker to protect populations.

The second reason why the vaccine industry should investigate the responsiveness of the development and manufacturing process is more about business and profitability of the industry. Moalla et al. find that in the vaccine industry there is a "winner-take-all" strategy. For a vaccine development company to be profitable they need to try and be the first to have a fully approved vaccine that is available to the medical community. The Moderna and Pfizer 2021 Quarter 3 business reports show demonstrate this profitability. Pfizer was the first company to have a SARS-CoV-2 vaccine approved for emergency use authorization (EUA) and subsequently the first to have full approval in the United States. Pfizer reports that their Q3 revenue from their SARS-CoV-2 vaccine to be $12.977 billion (Pfizer Inc., 2021). Moderna, who was the second company to have EUA, Q3 profits was $5.0 billion (Moderna, Inc., 2021). This difference in revenue shows the financial benefit to being responsive to a sudden need in the market such as that of a vaccine during a pandemic.

Chapter 2
Review of Literature

Responsiveness of Manufacturing

The first step to be able to develop a responsiveness model for pharmaceutical manufacturing is to define responsiveness in terms of manufacturing. This will be important in determining what factors will need to be considered when determining how responsive the vaccine development and manufacturing process is.

Ebrahim et al. look at responsiveness in terms of manufacturing operations. They show that the term responsiveness has been viewed in a general sense such as the time it takes for a company to deal with a customer's request. This general definition has evolved to a more specific definition referring more to manufacturing which defines responsiveness as, "the ability of a manufacturing company to respond quickly to customer demands and market changes". Ebrahim et al. simplify the overall definition as, "time to respond". (Ebrahim, Ahmad, & Muhamad, 2014)

Holweg researches the concept of responsiveness and creates dimensions or factors that have to do with manufacturing and supply chain and then looks at them in two different industries, the automotive and electronics industries. Holweg finds several definitions that are similar to Ebrahim et al. definitions. Holweg utilizes a definition of responsiveness from researchers Kritchancai and MacCarthy. This defines responsiveness as, "the ability to react purposefully and within an appropriate time-scale to customer demand or changes in the marketplace, to bring about or maintain a competitive advantage." Holweg builds on this definition by including flexibility of the manufacturing system on how it becomes responsive. Holweg's definitions of flexibility and responsiveness are below.

> Flexibility is a generic ability to adapt to internal and/or external influences.

> Responsiveness is the ability of the manufacturing system or organization to respond to customer requests in the marketplace. To achieve responsiveness, certain types of flexibility are required of the manufacturing system itself, as well as of the supply and logistics subsystems. The types of flexibility required to achieve such responsiveness in the supply chain are contingent upon the system's structure and environment. (Holweg, 2005)

These definitions of responsiveness all have some similarities. They all refer to a change in customer demands or environmental changes. These constantly changing customer demands and environments is the reason why being responsive in the various industries is seen as being a competitive advantage. This changing demand usually has two parts, the actual demand or quantity of a product that is needed and the desired time that customers are willing to wait for the certain product. Holweg uses a metric developed by Hal Mather called the P/D ratio to explain why a certain manufacturing and fulfilment strategy may need to be used to meet the time desires of customers (Holweg, 2005). The "P" in the P/D ratio refers to the production system response time and the "D" in the ratio refers to the customers' willingness to wait. Holweg explains that Mathers uses this comparison of these two factors to determine if a company should consider various fulfilment strategies such as make to order, assemble to order, or engineer to order (Holweg, 2005).

Holweg identifies three dimensions of responsiveness in which being flexible in the dimensions can lead to being responsive in manufacturing. These three factors are flexibility of product, process, and volume (Holweg, 2005).

The product dimension refers to some of the specifics of the product that is being produced. Every product that needs to be manufactured is going to be different. By understanding the product that needs to be manufactured one can better understand how an industry may be able to be more responsive. For example, being responsive in the automotive industry will be quite different than being responsive as in the pharmaceutical industry. Some metrics and considerations can be used to evaluate this dimension of

responsiveness can be customization points, whether the product is integrated, modular or fully custom, and potentially even a product life cycle analysis.

The next dimension Holweg refers to is the process dimension. This dimension has to do with the specific nature of the manufacturing processes, supply chain and logistics of the product. Things to consider in this dimension would be supplier lead times, types of manufacturing, manufacturing cost, machine changeover time, and other manufacturing metrics that may be specific to the process.

The last dimension that Holweg considers is volume. This dimension has to do with changing customer demand, where the decoupling point is in the supply chain, and customer expectations. The volume dimension is the main driver in being able to meet the quantity of demand.

Holweg states that considering these factors to be aware of and create a more responsive product development process can help provide customers with the products they want within a desired timeframe. Holweg states that there is not a single way for a supply chain to be responsive and a different approach must be taken for different industries and products (Holweg, 2005).

Ebrahim et al. proposes a different model for responsiveness in manufacturing operations which considers various drivers or reasons for being responsive, enablers and measures to be used when looking at the manufacturing operations, and then impacts of being responsive. The first part of the model involves the drivers or reasons for being responsive. Ebrahim et al. identify the various drivers as customers, suppliers, competitors, and global factors. The customer, suppliers, and competitor drivers fill similar roles to what Holweg describes with the changing customer demands, supplier interactions, as well as being able to create a competitive advantage being reasons for being responsive. Ebrahim et al. note in their model various global factors for being drivers for being responsive. These factors can include social changes, technology advancements, economic, and political changes.

Based on current research there are some models to consider when developing a quantifiable model to analyze the responsiveness performance of the vaccine development and manufacturing process. Both Ebrahim et al. and Holweg stress the importance of companies to be responsive in today's manufacturing environment. This model should be able to analyze the responsiveness in the vaccine manufacturing and other manufacturing industries.

Vaccine Development and Manufacturing

Just like with many industries, there has been a lot of research done in the vaccine and pharmaceutical development and manufacturing industry on the specific intricacies of the industry and can be improved. It is difficult to fully consider and encompass the entire supply chain and factors that may affect the vaccine development process so this thesis will cover some general themes that have been identified in research.

Vaccine Research and Development

Just like many products the road starts with research and development. In the vaccine industry this research and development occurs in a laboratory to categorize and research the disease, develop vaccine candidates (prototypes), test on animals and more. This research and development of vaccine candidates can vary in the length of time to complete due to what is trying to be achieved in the vaccine. Once a valid vaccine candidate is created a company can begin to move into more testing on animals and then eventually to clinical trials of the vaccine in humans (U.S. Food & Drug Administration, 2020). The clinical trial process also can vary in the length of time to work through based on the results. In cases of the vaccine candidate not passing clinical trials the development company would have to go back to the research and development phase to create a new vaccine candidate. This step of the vaccine development process can be quite expensive and take a long time based on the pathology of the disease and desired immune response of the vaccine. Towards the end of the clinical trial process if things are looking positive for the vaccine candidate the company can begin working with regulatory agencies to receive approval for the product and manufacturing methods. In the United States the Food and

Drug Administration oversees the approval and regulation of vaccines (U.S. Food & Drug Administration, 2020).

Vaccine Manufacturing Process

Gomez et al. find that more than 1 billion doses of vaccines that are manufactured are given to healthy people each year to protect them from diseases. They state that this is one of the driving factors that causes the industry to be extremely regulated and monitored as to not cause harm to those people. Gomez et al. lay the foundation for safe and consistent vaccine manufacturing based on four competencies (Gomez & Robinson, 2018).

1. The manufacturing process that defines how the product is made
2. The compliance of the organization to successfully complete that process
3. The testing of the product and supporting operations
4. The regulatory authorization to release and distribute the product

If an organization can be competent in these areas, they have the capability of producing a safe vaccine.

The fourth competency of meeting regulatory authorizations is necessary to begin the manufacturing process. Gomez et al. investigate various pharmaceutical regulatory agencies to develop the following four key elements of the approval process (Gomez & Robinson, 2018).

- Preparation of preclinical materials for proof-of-concept testing in animal models' manufacture of clinical materials according to current good manufacturing practices; and toxicology analysis in an appropriate animal system.
- Submission of an investigational new drug (IMD) application for submission to Food and Drug Association (FDA) for review.
- Testing for safety and effectiveness through clinical and further nonclinical studies (Phase I to Phase III clinical studies).

- Submission of all clinical, nonclinical, and manufacturing data to the FDA and European Medicines Agency (EMA) in the form of a Biologics License Application (BLA) for final review and licensure.

These approval elements can take about on average about 10 months for a vaccine to be approved and thus move on to being able to produce and manufacture the drug (Gomez & Robinson, 2018). Should any changes need to be made due to the manufacturing process some of the regulations will need to be reevaluated by regulation agencies. The FDA lists unexpected safety issues, manufacturing issues, or failure to prove a drug's effectiveness as the most common reasons for the denial of a drug application.

Gomez et al. then describe the basics of manufacturing of vaccines. In general, the vaccine manufacturing process happens in five steps. First includes a cell culture/fermentation which involves the initial creation of the desired antigen. Next is the isolation process to separate the antigen from the environment that was used in the previous step. Following the isolation process, the separated antigen must be purified to be used in the vaccine. The purified antigen then is combined with other ingredients to make the vaccine more stable in the formulation step. The last step involves the preservation process which includes the fill and finish operations like sterilizing and filling vials, packaging, and preparing storage solutions (Gomez & Robinson, 2018). The combined vaccine research and development process and manufacturing can be seen in Figure 3.

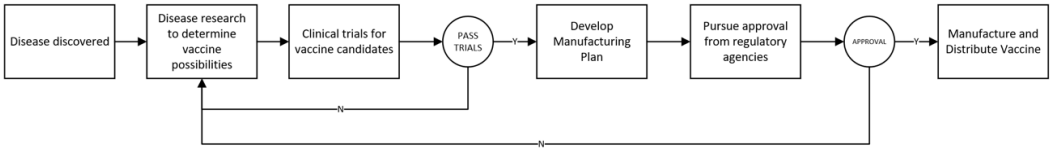

Figure 3 : Vaccine Development and Manufacturing Process

Vaccine Manufacturing Difficulties

Moalla et al. describes some of the reasons why vaccines are different due to the nature of the product manufacturing. They describe that the biological manufacturing process of

antigens in vaccines is inconsistent and variable (Moalla, Bouras, & Neubert, 2007). This variability is something that makes it more difficult to design a manufacturing process that can create the desired product. Vaccine manufacturing facilities utilize rigorous quality testing throughout the process to ensure the final vaccine meets regulatory requirements (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016).

The manufacturing of pharmaceuticals including vaccines is monitored by regulatory agencies. In the United States the regulatory agency is the Food & Drug Administration (FDA). The FDA regulates the quality of pharmaceutical manufacturing using the Current Good Manufacturing Practice (CGMP) regulations (U.S. Food & Drug Administration, 2020). The CGMP regulations include regulations on things like cleaning and sterilization of equipment between manufacturing runs, the types of equipment and interactions that can come into contact with the pharmaceutical (Shukla & Gottschalk, 2013). The FDA approval process is defined under a framework that includes the analysis of the target condition and available treatments, assessment of benefits and risks from clinical data, and finally the strategies for managing the associated risks of the drug (U.S. Food & Drug Administration, 2022). The FDA states that an approval of a drug means that the drug, "is determined to provide benefits that outweigh its known and potential risks (U.S. Food & Drug Administration, 2022). As stated before this regulatory process can be accelerated by the agency that oversees the

Contract and Development Manufacturing Organizations

The vaccine development and manufacturing process can be quite complicated, have a high cost and take up to several years to complete. Because of this pharmaceutical companies have looked to contract and development manufacturing organizations (CDMO) to assist with various parts of the process. A CDMO is an organization that a pharmaceutical company will contract to help with one or multiple steps of the vaccine (or other pharmaceutical) development and manufacturing process (Pricewaterhouse Coopers GmbH, 2019). This means a CDMO can assist with any part of the development and manufacturing process from running clinical trials all the way to the manufacturing and

distribution of the product. A CDMO will usually not be contracted to do initial research on a pharmaceutical. CDMO's can be specialized in processes or parts of processes that are related to a specific type of pharmaceutical such as injected vaccines, or solid pharmaceuticals. This is like how various contractors may be contracted to work on a specialized part of a construction project such as plumbing, or electrical. Figure 4 shows where CDMO's can operate within the vaccine development and manufacturing process. One of the main areas that CDMO's operate is called the fill and finish operations. Martagan et al. describe fill and finish operations as the specialized handling of manufactured bulk product and dividing it into the final commercial form (Martagan, Akcay, Koek, & Adan, 2021). This process usually involves steps such as filling vials, assigning labels, and packaging vials for storage and transportation. Throughout this process the sterility and ideal environmental conditions for the product must be maintained for the product to remain safe. (Martagan, Akcay, Koek, & Adan, 2021)

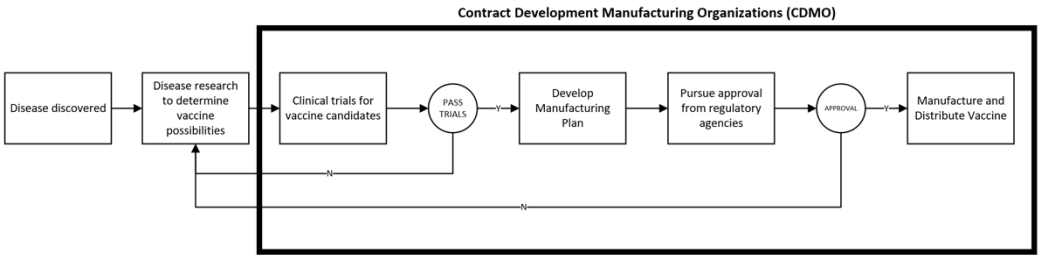

Figure 4 : CDMO in the Vaccine Development and Manufacturing Process

Vaccine Supply Chain

Understanding some elements of the vaccine supply chain can help us identify where the industry does well and where there are some weak points. Identifying these areas can help provide information how the industry responds to a pandemic which can put extra pressure on that supply chain. Lemmens et al. writes that the vaccine supply chain and manufacturing do not behave like normal goods even in normal times (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). Lemmens et al. describe that a normal supply

chain design consists of various elements including suppliers, plants, distribution centers, and customer markets.

Lemmens et al. include some characteristics that factor into the supply chain network of vaccines which include, allocation, location, limited shelf life, cold chain distribution, production capacity planning, batch sizing, and uncertainty (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). Lemmens et al. attempt to answer that a combination of these factors is what can make the vaccine supply chain difficult.

Allocation of vaccines refers to vaccine producing companies' availability to get their product to where it is needed whether that be in a highly populated area or where people are more spread out (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). This is an important factor because of the nature of the product which goal is to protect a population against a disease. If the company cannot allocate the vaccines to where it needs to be then the population will still be at risk.

The allocation factor leads into the next two factors: Location of manufacturing, and Distribution. These factors can help solve the allocation issues that the supply chain may undergo. Lemmens et al. explain that the decision of where to manufacture a vaccine is important to the allocation and distribution strategy of a vaccine. Once that strategy is determined it is costly to change due to the expensive nature of manufacturing processes and facilities (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). Distribution can also help with the allocation factor for vaccines. Not every vaccine is the same and some require special distributions to ensure that the vaccine is viable. Vaccines may have a short shelf life and need to be delivered quickly or distribution methods may need to accommodate for cold storage of the vaccine so that it stays useable (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). Contract development and manufacturing organizations may help a vaccine developer address some of these factors by specializing in some of these areas by helping with fill and finish operations of vaccines, working on packaging and shipping methods with shipping companies (Pricewaterhouse Coopers GmbH, 2019).

The next two areas that Lemmens et al. discuss as a factor in the difficulty of the supply chain is the production capacity planning and the batch sizing. Capacity planning in the vaccine is normally built around routine cycles of demand (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). The long lead time required to make changes to capacity makes it difficult to quickly change and adapt to a surge in demand of a vaccine. Batch size of a production run is also a factor when it comes to the difficulty of the vaccine supply chain. Whenever a change is made to address the batch size of a vaccine the process needs to be verified to ensure the result of a safe, quality product (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016). This means if a company needs to increase batch size to account for an increase of demand or if the formulation of the vaccine needs to be slightly adjusted (say for a new mutation of a virus), a new manufacturing process needs to still meet regulatory standards. Meeting these standards may be difficult, time consuming, and costly for a simple increase of batch size.

Chapter 3
Methods

After performing the literature review, there are two important parts to a company's ability to be responsive, the company responsiveness performance measures, and customer factors. These two aspects are important to developing the evaluation of how responsive a company's vaccine supply chain is.

Customer Factors

Previous research on manufacturing responsiveness describes that a key element of responsiveness is the customer. In product development, including vaccine development, there is always going to be a customer. The consideration of what the customer wants is one of the driving factors towards what the final market product is. On top of considering what the customer wants, a company needs to also consider how long the customer is willing to wait for the product. This factor is key for a company to understand how

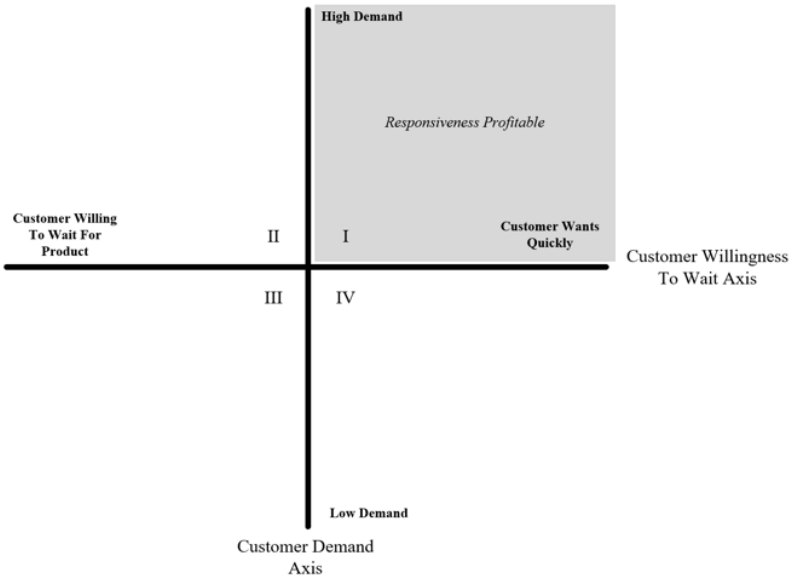

Figure 5 : Customer Factors Chart

responsive they will need to be. A similar line of thought can be used to that of Mathers P/D ratio for determining manufacturing and fulfilment strategies that Holweg describes (Holweg, 2005). Rather than comparing the production response time to the customer willingness to wait as described, the customer demand quantity can be compared to the customer willingness to wait. If the customer is willing to wait for a product, then a company can afford to be less responsive without losing too much profit. Whereas if a customer is not willing to wait for a product as long then it may be worth it for a company to be more responsive to meet those customer wants. The other customer factor involves the amount of customer demand for a product. If there is a high demand for a product the potential profit off that product is going to be higher than that of a product that has low demand. These two factors, customer willingness to wait and customer demand, can be plot against each other on a chart with the customer willingness to wait on one axis going from "can wait" to the "customer not willing to wait", and customer demand on the other axis going from "high demand" to "low demand". This chart can be seen in Figure 5. Quadrant one of this chart is where there is high customer demand, and the customer is not willing to wait. If a product is in this quadrant, it may be extremely profitable for a company to provide that product quickly which would mean they would need to be more responsive to that demand. In the case of the vaccine industry, the SARS-CoV-2 vaccine was a product that was in very high demand and the customers wanted it as soon as possible which placed this product in quadrant one of our willingness to wait vs. customer demand chart. The combination of these two factors shows that with any product it will ultimately be the customer that decides if a company is responsive enough or not to produce the product.

Company Responsiveness Measures

The second part of the model involves looking at the elements of a company's supply chain and development cycle that has an impact on responsiveness. The purpose of these measures is to be able to evaluate the performance each of the supply chains in terms of responsiveness. The developed measures in Table 1 provide responsiveness measures for the vaccine industry so they can be used to evaluate the responsiveness performance of

several companies during the SARS-CoV-2 pandemic. These measures are based on Holweg's three dimensions of responsiveness of product, process, and volume as well as the research done on the vaccine industry. These measures can then be organized into different categories and drivers to evaluate the process in a variety of different ways. Figure 6 shows the combination of the customer and company factors that ultimately will determine if a company is responsive or not.

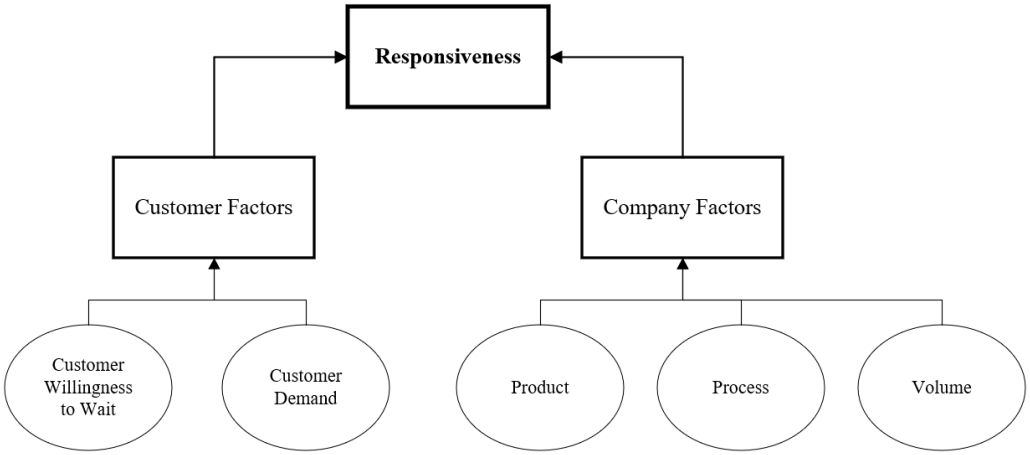

Figure 6: Responsiveness Factors

Table 1: Responsiveness Performance Measures

Product/Process/Volume	Performance Measure	Measure Code	Measure Justification	Category/Drivers
Product	Type of Vaccine	TYP	Different types of vaccines have different development and manufacturing times. The type of vaccine is not used directly in the responsiveness analysis but is useful to see if different vaccines can be more responsive. (Rosa, Prazeres, Azevedo, & Marques, 2021)	Product Details
Product	Average time for experimental dose for type of vaccine	ATED	The average time for experimental doses can give insight into how long the development time will take. This measure shows the time for a company to iterate a single vaccine candidate. Faster iteration of vaccine candidates can lead to a quicker time to get to clinical trials. (Johns Hopkins University of Mediine, n.d.)	Product Details
Product	Average time to market for type of Vaccine	ATM	The average time to market is like the average time for experimental doses but this will include the clinical trial process and manufacturing development process. (Gomez & Robinson, 2018)	Product Details

Product	Regulatory Agency Involvement	RAI	The pharmaceutical industry is regulated to maintain the safety of the products. The compliance with regulatory organizations is an important part to the vaccine development process. (Gomez & Robinson, 2018)	Product Details
Product	Similarity to existing Product Offerings	SIM	If a company has similar products to the one that needs to be produced in a responsive way, then they will be able to respond quicker than a company that is developing a completely new product.	Product Details
Process	Resource: Equipment	RES-EQU	Resources are important for a company to maintain its operations. Collier et al. identify several resources that a company manages. These resources include equipment, facilities, materials, information, technical knowledge, skills, and people. (Collier & Evans, 2017) The availability of these resources can help a company be more responsive.	Company
Process	Resource: Facilities	RES-FAC		
Process	Resource: Materials	RES-MAT		
Process	Resource: Information/Technical Knowledge	RES-INFO		
Process	Resource: Skills/People	RES-SKL		
Process	Utilization of CDMO for Research Operations	CDMO-R	Receiving specialized assistance on various parts of the vaccine development process and supply chain can help vaccine companies respond quicker. This specialization can help with some of the uncertainties in the vaccine supply chain that Lemmens et al. describe in their paper. (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016)	Product Details
Process	Utilization of CDMO for Fill and Finish Operations	CDMO-FF		Supply Chain
Process	Utilization of CDMO for Manufacturing Operations	CDMO-MO		Manufacturing
Product	Need for Unique Storage/Transportation Requirements (ex: Cold Storage)	UNQ	If a product is needed quickly and the transportation and storage infrastructure is drastically different it will need to be developed, which can affect the development times. (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016)	Product Details

Process	New/Different Manufacturing Techniques	NEW	Similar to the previous measure, if new manufacturing techniques need to be set up or established this can add time to the development process. (Lemmens, Decouttere, Vandaele, & Bernuzzi, 2016) New manufacturing techniques also must be safe and adhere to all regulatory agency policies. (Gomez & Robinson, 2018)	Manufacturing
Process	Downstream supply chain flexibility	DSCF	The downstream supply chain including fill and finish operations, transportation, and distribution can affect the responsiveness of an industry. (Ebrahim, Ahmad, & Muhamad, 2014)	Supply Chain
Process	Upstream supply chain flexibility	USCF	Sourcing adequate high-quality materials for a product when there is a sudden change in demand can help a company respond quicker. (Ebrahim, Ahmad, & Muhamad, 2014)	Supply Chain
Process	Manufacturing Process (MP): Risk of bottlenecks in process	MPBN	There are varying risks of bottlenecks in manufacturing processes. High risk of bottlenecks in the manufacturing process will slow down the process. Knowing where these bottlenecks are can help with maintaining manufacturing objectives to meet customer demand. (Rosa, Prazeres, Azevedo, & Marques, 2021) (Collier & Evans, 2017)	Manufacturing

Process	MP: Ease of Changing manufacturing process	CHMP	Not only are the products in the pharmaceutical industry highly regulated, but the manufacturing processes are also regulated to ensure the safe manufacturing of medical products. Because of the regulations on manufacturing, the time it takes to change the manufacturing process can affect the ability to make quick, flexible changes. (Shukla & Gottschalk, 2013)	Manufacturing
Process	MP: Changeover time	MPCT	The changeover time is the time it takes to switch a manufacturing process from one process to another. This can also include the resetting of the vaccine manufacturing process to maintain sterility. (Jacobs & Chase, 2018) A longer changeover time can reduce responsiveness.	Manufacturing
Volume	Expansion of Manufacturing Capability (Scale Up Capability)	EMP	In the case of an unexpected high demand product that is needed quickly there may be a need to scale up manufacturing capabilities. (Soni & Kodali, 2010) This measure is used to evaluate the manufacturing process.	Manufacturing
Volume	MP: Operation Time of Manufacturing	OTMP	The operation time of the manufacturing process us used to evaluate the manufacturing process. (Jacobs & Chase, 2018) (Collier & Evans, 2017)	Manufacturing

Model Details

To evaluate the responsiveness performance of the vaccine supply chain an internal benchmarking method can be used to evaluate similar supply chains within a single company (Soni & Kodali, 2010). Soni and Kodali utilize a multi-attribute decision model method called performance value analysis (PVA) along with a strength, weakness, opportunities, and threats (SWOT) analysis to compare similar global supply chains within a single textile & apparel company. Their model will be adjusted to evaluate and compare the performance of responsiveness with various vaccine supply chains for similar products. The previously developed responsiveness performance measures will be used to evaluate the model based on the analysis objectives.

Performance Value Analysis Method

Below is the methodology for performing the PVA used to evaluate the responsiveness performance measures (Soni & Kodali, 2010).

1. Define the problem and determine the objective.
2. Identify the alternatives (a_i) available. (The alternatives are the supply chains that are being evaluating for responsiveness)
3. Determine the performance indicators/measures (c_j) that govern the problem.
4. Classify the performance indicators/measures into significant categories/drivers such as fields of measurement.
5. Classify the performance indicators into direct (performance grows while measurement increases) and indirect categories (performance grows while measure decreases).
6. Form the performance matrix, i.e. co-efficient e_{ij} related to the performance indicator c_j (j = 1, 2, …, j) and the alternative a_i (i = 1, 2, …, i)
7. Quantify the qualitative attributes using the scales on each performance measure.
8. Absolute weightage w_j on a suitable scale is assigned for each performance indicator reflecting the normative judgement of the decision maker.

9. Form the normalized performance matrix. It is transforming the initial performance measure in a score/weight for easier interpret based on the value function f_j for each performance indicator (c_j) as follows:
    - Direct category (when performance increases while measure increases):

      $p_{ij} = \frac{e_{ij}}{\max(e_j)}$ for each alternative a_i related to attribute c_j.
    - Indirect category (when performance grows while measure decreases):

      $p_{ij} = \frac{\min(e_j)}{e_{ij}}$ for each alternative a_i related to attribute c_j.
10. Obtain the relative weightage for each performance indicator (c_j) from absolute weightage w_j:

    $$\bar{W}_j = \frac{w_j}{\sum w_j} \quad \text{such that} \quad \sum \bar{W}_j = 1$$
11. Obtain partial performance measure Z_{ij} by multiplying relative weightage $\bar{W}_j$ of performance indicator to each of its row members (alternatives), ie. p_{ij} as:

    Partial performance of *j*th attribute: $Z_{ij} = p_{ij} \times \bar{W}_j$ (i = 1, 2, …, i)
12. Aggregate the partial performance measures for each alternative as: overall measure (N_i) of alternative a_i is the sum of Z_{ij}

    $$N_i = \sum_{j=1}^{J} Z_{ij}$$

Application of Model

The application of this model is slightly different than what Soni and Kodali used for the analysis of a textile supply chain. This section will describe some of the considerations taken for the use of the PVA responsiveness model.

Step one of the processes is to define the problem and objectives (Soni & Kodali, 2010). This process will be used to evaluate the responsiveness of various vaccine supply chains to see where some areas can be improved with the end goal of being more prepared for the next pandemic level event where a vaccine or other pharmaceutical needs to be created.

Step two says to define the alternatives (Soni & Kodali, 2010). The alternative supply chains that will be analyzed are BioNTech as if they created their own vaccine, Pfizer and BioNTech partnering to create a vaccine and Johnson and Johnson developing a vaccine. These supply chains were selected so that the analysis objectives can be met. The analysis objectives were to evaluate how the partnership between the Pfizer and BioNTech affected their ability to produce a vaccine rapidly and to compare how the type of vaccine impacts the responsiveness too. By selecting these alternatives, the analysis of the objectives is possible.

Step three says to determine the performance indicators and measures that will govern the problem (Soni & Kodali, 2010). To evaluate the performance of responsiveness the company responsiveness factors that were based on Holweg's Product, Process, and Volume research will be used (Holweg, 2005). Each of these factors was given a metric to evaluate each supply chain on it. Steps four and five involve classifying each of the performance measures into significant categories/drivers and to assign if they are direct or indirect category. For the significant categories/drivers, the measures can evaluated in two ways. In the first way, the measures will be split up the categories into Holweg's three responsiveness dimensions of product, process, and volume. The second way the measures can be split up is by assigning them into more detailed categories of, product details, manufacturing, company, and supply chain categories. These detailed categories were chosen to see in more detail which areas of the vaccine supply chain can be improved in terms of responsiveness. Assigning the measures into direct or indirect categories based on how the measure is scored was done the same way as in Soni and Kodali's methods. A measure that is direct indicates that a higher score will mean the measure is better for responsiveness. An example of a direct category would be the upstream and downstream supply chain flexibility (USCF & DSCF) measures. In these categories a higher score indicates that a company's corresponding upstream or downstream supply chain is more flexible. Conversely, a measure that is indirect indicates that a lower score will mean the measure is better for responsiveness. An example of an indirect category in this model is the new manufacturing techniques measure (NEW). In this measure a lower score indicates that there are not many new manufacturing techniques that need to be considered,

and thus a company will be able to quickly adjust manufacturing operations. This lower score indicates a higher performance in responsiveness. The description of each of these metrics and if it is direct or indirect is given below in Table 2. There are several ways to evaluate these measures. Some measure uses a scaling scoring system, others will use direct manufacturing process evaluation data, and others will be a yes or no answer. The responsiveness measures that use a scale scoring system will be scored on a 1-5 scale as opposed to a larger scale like 1-10 system to simplify the decision-making process and avoid the ambiguity of the differences of one score vs. another. Future work can be done to come up with defined methodologies to use a more divided metric. An evaluation of these metrics will determine the score of the measure. Table 2 will also describe how to score using the scaling system.

Table 2 : Description of Responsiveness Metrics

Company Responsiveness Performance Measure	Description of Metric	Direct or Indirect
TYP	Description of Type of Vaccine (Viral Vector, mRNA, or other type of vaccine) This metric is used for comparison of supply chains and will not be used for the PVA.	N/A
ATED	Average Time for experimental dose (In months)	Indirect
ATM	Average Time from conception to market (In months)	Indirect
RAI	Scale 1-5 (1 = Low Regulatory Agency Involvement, 3 = Moderate Regulatory Agency Involvement, 5 High Regulatory Agency Involvement)	Indirect
SIM	Scale 1-5 (1 = No similar products, 3 = Some similarities, 5 = Very similar products, minimal changes needed)	Direct
RES-EQU	Scale 1-5 (1 = Resource not readily available and may be difficult to acquire, 3 = Resource may be available and/or may need some work to acquire, 5 = Resource readily available)	Direct
RES-FAC		
RES-MAT		
RES-INFO		
RES-SKL		
CDMO-R	Yes or No (Does the supply chain for this product utilized a CDMO for the described parts of the supply chain?)	Direct
CDMO-FF		
CDMO-MO		

UNQ	Scale 1-5 (1 = No unique storage/transportation requirements, 3 = Some unique storage/transportation requirements, 5 = Significantly unique storage/transportation requirements)	Indirect
NEW	Scale 1-5 (1 = Not very many new processes in manufacturing, 3 = Some new techniques/technologies, 5 = Many new manufacturing techniques)	Indirect
DSCF	Scale 1-5 (1 = Low Flexibility, 3 = Moderate Flexibility, 5 = High Flexibility)	Direct
USCF	Scale 1-5 (1 = Low Flexibility, 3 = Moderate Flexibility, 5 = High Flexibility)	Direct
MPBN	Scale 1-5 (1= Low risk of bottleneck in process, 3 = Moderate risk of bottleneck in process, 5 = High risk of bottleneck in process	Indirect
CHMP	Scale 1-5 (1 = Difficult to change process, 3 = Moderate to change process, 5 = No difficulties changing process)	Direct
MPCT	Changeover time (In whatever unit makes sense for evaluation)	Indirect
EMP	Scale 1-5 (1 = Difficult to scale up, 3 = Moderate difficulty to scale up, 5 = High scale up capability)	Direct
OTMP	Operation time (In whatever unit makes sense for evaluation)	Indirect

The analysis chapter will look at the scores assigned for each supply chain and perform the PVA analysis to gain some insight to the responsiveness of the various vaccine development supply chains.

Chapter 4
Analysis

The analysis will look at the responsiveness measures and metrics to perform the PVA analysis described in the previous chapter. The first step in performing the performance value analysis is to create our performance matrix by assigning scores to each measure. The ideal use of this methodology is for internal or external benchmarking to see how responsive a company is and where they may be able to improve.

In an ideal scenario the person/company performing this responsiveness analysis would have internal manufacturing and company data and would be able to carefully consider each measure to assign appropriate values. Due to the ongoing nature of the SARS-CoV-2 pandemic some data may be difficult to acquire that would make this analysis fully accurate. The available data from company and industry reports will be used to create estimates on the relative performances between the supply chains being investigating. In some cases, the detailed manufacturing performance measures will not be able to be comfortably estimated so those measures will need to be removed from the analysis. Based on this limitation the results of this analysis will not show the real-life performance of these supply chains and will not represent real-world due to my interpretations of some of the measures. Despite these limitations this thesis should still provide a foundation to analyze the responsiveness of these companies and show the workings of the responsiveness analysis model.

Creation of Performance Matrix

The first thing to do will be to create the blank matrix of scores with our alternative supply chains (a_i) and the performance indicators (c_j). This blank matrix is shown in Table 3. This matrix is set up in a way that it will give incite to the problem that is described in step 1 of the PVA methods. In this study the evaluation will be between three different supply chains. The responsiveness analysis is useful because the product being considered, a SARS-CoV-2 vaccine, is of high demand and is needed quickly. By setting up the matrix

like this the analysis will be able look at how various factors affect the responsiveness of these products and how they were developed.

Filling in the Performance Matrix

The next step is to perform an analysis of the various measures for the different supply chains. As stated before, company and industry reports will be used to come up with values that represent relative performance of each of the supply chains. The following sections will describe how each performance measure was scored for each supply chain.

Table 3 : Blank Performance Matrix

			Supply Chain Alternatives (a_i)		
	Significant Category/Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson and Johnson
Performance Indicators/Measures (c_j)	Product Details	TYP			
		ATED			
		ATM			
		RAI			
		SIM			
		UNQ			
	Company	RES-EQU			
		RES-FAC			
		RES-MAT			
		RES-INFO			
		RES-SKL			
	Manufacturing	NEW			
		EMP			
		MPBN			
		CHMP			
		CDMO-MO			
	Supply Chain	DSCF			
		USCF			
		CDMO-FF			

Product Details Scores

For the product details section, following performance measures were used: type of vaccine, average time for experimental dose, average time to market, regulatory agency involvement, similarity to existing product offerings, and the need for unique

storage/transportation requirements. The utilization of CDMO's for research operations will not be used because this information will not be available to find.

The type of vaccine measure is not one that is assigned a numerical value but is there as a note to compare potential different vaccine technologies. In the pandemic situation that is being evaluated, Johnson and Johnson is a viral vector vaccine, BioNTech and the Pfizer-BioNTech partnership are mRNA vaccines. (Centers for Disease Control and Prevention, 2021) (Centers for Disease Control and Prevention, 2022)

For the average time to experimental dose, Johnson and Johnson utilizes a viral vector technique in which the time it takes to create a safe experimental dose takes longer. Because of this I will use an average time for developing the experimental dose as 6 months which aligns with a typical development cycle using tried and tested techniques (Johns Hopkins University of Mediine, n.d.). BioNTech utilizes a type of vaccine technology called mRNA vaccines. According to company reports an experimental dose can be generated within a week which would put the value at 0.2 months. (BioNTech Manufacturing GmbH, 2022) Finally, because Pfizer and BioNTech utilized the mRNA technique the score for that supply chain will also be 0.2 months.

The average time to develop a vaccine from conception to market for traditional viral vector vaccines is 5-10 years to develop (Johns Hopkins University of Mediine, n.d.). This is because of many things including regulatory agencies, developing manufacturing plans, and clinical trials. The Pfizer-BioNTech vaccine received full FDA approval in about 20 months from when research began. I will use this value for the BioNTech and Pfizer-BioNTech supply chains. As of writing this paper the Johnson and Johnson vaccine does not have full FDA approval and is still under emergency use authorization so the traditional development time that is described by Johns Hopkins University of Medicine will be used of 7 years or 84 months as the value.

In the pharmaceutical industry, regulatory agencies are important to maintain the safe development and manufacturing of vaccines and other pharmaceuticals. (Gomez & Robinson, 2018) These regulatory agencies are quite involved in ensuring safe practices

and as such all three supply chains will be assigned a 5 for high regulatory agency involvement.

Johnson and Johnson developed a vaccine using technology and manufacturing processes that they were already familiar with because of this Johnson and Johnson will be scored a 5 for the similarity to other product offerings. For BioNTech and the Pfizer-BioNTech partnership they were familiar with the science of the mRNA vaccines, but it had never been manufactured and developed for large production. For this reason, these two supply chains will be scored as a 3. (Rosa, Prazeres, Azevedo, & Marques, 2021)

The last responsiveness performance measure for product details is the unique storage and transportation requirements of the product. The Johnson and Johnson vaccine does not require any unique storage or transportation techniques different from what their normal supply chain offers. The Pfizer-BioNTech vaccine does require significantly more cold storage and transportation from their normal products. (Centers for Disease Control and Prevention, 2021) (Centers for Disease Control and Prevention, 2022)

Table 4 : Product Details Responsiveness Scores

			a_i		
	Significant Category/Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson & Johnson
c_j	Product Details	TYP	mRNA	mRNA	Viral Vector
		ATED	0.2	0.2	6
		ATM	20	20	84
		RAI	5	5	5
		SIM	3	3	5
		UNQ	Y	Y	N

Company Scores

For the company section, the following performance measures are looked at: resources-equipment, resources-facilities, resources-materials, resources-information/technical knowledge, and resources-skills/people.

For many of these company resources including equipment, facilities, materials, information, technical knowledge, skills, and people the various companies will be investigated using company reports and industry trends to determine their relative comparative scores when it comes to their ability to respond to an unexpected, high need of a product quickly.

The first company investigated is BioNTech. As stated in the background information, BioNTech is a smaller company and therefore will have lower scores in the equipment, facilities, and materials resource measures than that of Pfizer and Johnson and Johnson. BioNTech will be scored a three in equipment because they would have access to much of the equipment needed to develop a vaccine and its manufacturing process. Compared to Pfizer and Johnson and Johnson they will have less resources available to them so they will be scored those two measures as a one. Though BioNTech may be lacking in the facilities and materials they had been studying mRNA vaccines for much longer and were able to utilize that knowledge to develop a vaccine for SARS-CoV-2. Because of this BioNTech will be scored a five in both information/technical knowledge and skills/people.

Next, Johnson and Johnson's company responsiveness measures will be presented. Compared to BioNTech, Johnson and Johnson is a much bigger company with many resources that will allow them to be able to develop a vaccine. Due to the relative size difference of the Johnson and Johnson company and supply chain to that of BioNTech, Johnson and Johnson will be assigned a score of five for all these categories.

The last supply chain to look at is the Pfizer-BioNTech partnership as it pertains to the response to the SARS-CoV-2 pandemic. Pfizer, like Johnson and Johnson is a large company that has access to a lot of resources. Because of this the scores of the BioNTech equipment, facilities, and materials scores will be increased to five because Pfizer brings those elements to the partnership that the two companies have.

Table 5 : Company Responsiveness Scores

			a_i		
	Significant Category/ Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson & Johnson
c_j	Company	RES-EQU	3	5	5
		RES-FAC	1	5	5
		RES-MAT	1	5	5
		RES-INFO	5	5	5
		RES-SKL	5	5	5

Manufacturing Scores

For the manufacturing section, the following performance measures will be looked at: new/different manufacturing techniques, expansion of manufacturing capability, risks of bottlenecks in manufacturing process, ease of changing manufacturing process, and utilization of CDMO's for manufacturing operations. Due to the limitations of finding manufacturing information on the companies, the operation time of manufacturing, and changeover times as measures are unable to be used.

mRNA vaccines had never been used for such a wide scale vaccination effort. Rosa et al. explain that in general, the manufacturing of mRNA vaccines is simpler but scaling up some of the steps in the manufacturing process is something that would need to be improved (Rosa, Prazeres, Azevedo, & Marques, 2021). On top of this BioNTech and Pfizer have never produced an mRNA vaccine on this scale before and will need to develop the process so they will both be scored as a three in this measure. Johnson and Johnson have plenty of experience manufacturing viral vector vaccines and so they would not need any unique or new manufacturing techniques. Because of this, Johnson and Johnson will be scored a one in this area.

For the expansion capability of the manufacturing process, Pfizer-BioNTech and Johnson and Johnson vaccines will be scored as a three because they have more experience and resources scaling up manufacturing processes than BioNTech on their own. The BioNTech supply chain will be scored a one, because it would be more difficult for a

smaller company to scale up the manufacturing capacity to meet such a high demand that the SARS-CoV-2 pandemic required.

It is hard to tell without knowing the details of the specific manufacturing processes what the risks of bottlenecks are. Based on the research done by Rosa et al. and Gomez et al. there are some common bottlenecks in the vaccine industry such as approval processes and fill and finish operations. Each of these supply chains will be scored a two because there is some risk associated with the manufacturing process and it is not nonexistent (Rosa, Prazeres, Azevedo, & Marques, 2021) (Gomez & Robinson, 2018). This is a measure where the scoring could be improved if knowledge of the specific manufacturing details is aquired.

Gomez et al. explain that manufacturing of vaccines requires a Biologics License Application (BLA) that explains clinical, nonclinical, and manufacturing data and plans. This application must be approved by the FDA whenever the manufacturing process would change to maintain the safety of the vaccine. Because of this all three of the supply chains will be scored as a one in the ease of changing manufacturing process.

Finally due to the global nature of the SARS-COV-2 pandemic it would be difficult to produce the number of vaccines necessary internally. Pfizer and BioNTech utilize many CDMO's for manufacturing including Pfizer Centreone, which is Pfizer's internal CDMO (Pfizer Centreone, 2021). There are also reports that Johnson and Johnson also is utilizing CDMO's for the manufacturing of covid vaccines in order to meet the demand that is needed which includes a CDMO named Emergent BioSolutions, Inc. (Johnson and Johnson, 2020).

Table 6 : Manufacturing Responsiveness Scores

			a_i		
	Significant Category/ Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson & Johnson
c_j	Manufacturing	NEW	3	3	1
		EMP	1	3	3
		MPBN	2	2	2
		CHMP	1	1	1
		CDMO-MO	Y	Y	Y

Supply Chain Scores

For the supply chain section, the following performance measures will be used: downstream supply chain flexibility, upstream supply chain flexibility, and utilization of CDMO for Fill and Finish Operations.

Evaluating the supply chain flexibility both upstream and downstream is difficult to assign scores without knowledge of the specifics of the various supply chains. Because of this all of the supply chains will be scored a three for both the upstream and downstream flexibility. This is an area where more specific details of the supply chains will help assign better scores.

Company reports can be used to determine that Pfizer and Johnson and Johnson, have utilized CDMO's for fill and finish operations. (Johnson and Johnson, 2020) (Pfizer Centreone, 2021). I could not find information on whether BioNTech has used CDMO's for SARS-CoV-2 products so they will be marked that they have not utilized CDMO's in this way.

Table 7 : Supply Chain Responsiveness Scores

			a_i		
	Significant Category/ Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson & Johnson
5	Supply Chain	DSCF	3	3	3
		USCF	3	3	3
		CDMO-FF	N	Y	Y

Final Responsiveness Matrix and Weights

Once all the scores are made, combine the four category matrixes, and combine them to fill in the blank responsiveness matrix described that was Table 3. When they are combined, weights are assigned to each of the performance measures based on the normative judgement of responsiveness.

To weight each of the measures the researcher must determine which measures are going to have more of an impact on responsiveness. Information from Holweg and Ebrahim et al. was used to determine the weights for each measure. Higher weight scores indicate that the measure will be judged as impacting responsiveness more. The measures of ATED, ATM, are ranked five because they can show how long it may take for a company to develop a vaccine. RAI, all the company resource measures, and NEW, are weighted at a four because these factors also have a significant effect on a company's capability of fulfilling an unexpected, high demand product that is needed quickly, or have a significant impact on the operations of the vaccine industry. CHMP is weighted at a two because it has a smaller impact on the responsiveness of the entire process. It may affect how fast a company will be able to change manufacturing processes but if proper planning and considerations can be made it will impact the responsiveness less. The rest of the responsiveness measures are weighted at three due to their effect on responsiveness in the process.

These weights can be adjusted based on what measures a company feels impacts their responsiveness. For example, if a company feels that within the supply chains they are

analyzing, downstream supply chain flexibility is a significant factor they can weight the scores higher to reflect that analysis.

Table 8 : Final Responsiveness Matrix with Weights

			Supply Chain Alternatives (a_i)			
	Significant Category/Driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson and Johnson	Weights
Performance Indicators/Measures (c_j)	Product Details	TYP	mRNA	mRNA	Viral Vector	N/A
		ATED	0.2	0.2	6	5
		ATM	20	20	84	5
		RAI	5	5	5	4
		SIM	3	3	5	3
		UNQ	Y	Y	N	3
	Company	RES-EQU	3	5	5	4
		RES-FAC	1	5	5	4
		RES-MAT	1	5	5	4
		RES-INFO	5	5	5	4
		RES-SKL	5	5	5	4
	Manufacturing	NEW	3	3	1	4
		EMP	1	3	3	3
		MPBN	2	2	2	3
		CHMP	1	1	1	2
		CDMO-MO	Y	Y	Y	3
	Supply Chain	DSCF	3	3	3	3
		USCF	3	3	3	3
		CDMO-FF	N	Y	Y	3

After this matrix is created, the remaining steps of the performance value analysis can be performed. The next steps that need to be performed are step nine which in cludes normalizing the performance matrix and step ten which determines the relative weightage for each performance measure (Soni & Kodali, 2010).

When normalizing the matrix, it is important to utilize the correct formula based on whether the category is indirect or direct. This will ensure that the normalization considers if a higher score or lower score is better for a category. Soni and Kodali indicate that the normalization of the performance matrix is important because it will make the

interpretation of many different performance measures easier (Soni & Kodali, 2010). The results of steps nine and ten are displayed in Table 9.

Table 9 : Normalized Responsiveness Performance Matrix and Relative Weightage

Significant category/driver	Performance Measure	BioNTech	Pfizer + BioNTech	Johnson & Johnson	Weights
Product Details	TYP	N/A	N/A	N/A	N/A
	ATED	1	1	0.0333	0.0781
	ATM	1	1	0.2381	0.0781
	RAI	1	1	1	0.0625
	SIM	0.6000	0.6000	1	0.0469
	UNQ	1	1	0	0.0469
Company	RES-EQU	0.6	1	1	0.0625
	RES-FAC	0.2	1	1	0.0625
	RES-MAT	0.2	1	1	0.0625
	RES-INFO	1	1	1	0.0625
	RES-SKL	1	1	1	0.0625
Manufacturing	NEW	0.3333	0.3333	1	0.0625
	EMP	0.3333	1	1	0.0469
	MPBN	1	1	1	0.0469
	CHMP	1	1	1	0.0313
	CDMO-MO	1	1	1	0.0469
Supply Chain	DSCF	1	1	1	0.0469
	USCF	1	1	1	0.0469
	CDMO-FF	0	1	1	0.0469

After creating the normalized performance matrix and finding the relative weightage for each performance measure. The next step involves multiplying the relative weightage for each performance measure to each of the scores given to each supply chain alternative. This will yield the responsiveness partial performance measures for each significant category/driver. The result of this step is in Table 10.

Table 10 : Responsiveness Partial Performance Measures

Significant category/driver	Performance Measure	BioNTech	Pfizer + BioNTech Partnership	Johnson & Johnson
Product Details	TYP	N/A	N/A	N/A
	ATED	0.0781	0.0781	0.0026
	ATM	0.0781	0.0781	0.0186
	RAI	0.0625	0.0625	0.0625
	SIM	0.0281	0.0281	0.0469
	UNQ	0.0469	0.0469	0.0000
Company	RES-EQU	0.0375	0.0625	0.0625
	RES-FAC	0.0125	0.0625	0.0625
	RES-MAT	0.0125	0.0625	0.0625
	RES-INFO	0.0625	0.0625	0.0625
	RES-SKL	0.0625	0.0625	0.0625
Manufacturing	NEW	0.0208	0.0208	0.0625
	EMP	0.0156	0.0469	0.0469
	MPBN	0.0469	0.0469	0.0469
	CHMP	0.0313	0.0313	0.0313
	CDMO-MO	0.0469	0.0469	0.0469
Supply Chain	DSCF	0.0469	0.0469	0.0469
	USCF	0.0469	0.0469	0.0469
	CDMO-FF	0.0000	0.0469	0.0469

The final step of the performance value analysis is to sum each of the partial performance measures for each significant category/driver and each supply chain alternative. This final table is the aggregate indices for the responsiveness analysis. This is shown in Table 11.

Table 11 : Aggregate Indices for Responsiveness Analysis

Significant category/driver	BioNTech	Pfizer + BioNTech Partnership	Johnson & Johnson
Product Details	0.2938	0.2938	0.1306
Company	0.1875	0.3125	0.3125
Manufacturing	0.1615	0.1927	0.2344
Supply Chain	0.0938	0.1406	0.1406

This final aggregate indices matrix is what can give some insight into how these different supply chains performed relative to each other in response to the SARS-CoV-2 pandemic. The next chapter will investigate some of the results of this matrix to investigate some of the analysis objectives.

Chapter 5
Results

The initial performance value analysis methodology was proposed by Soni and Kodali to evaluate similar supply chains within a company to see which ones could be improved. By selecting performance measures that impact responsiveness in the vaccine industry the PVA analysis was able to do a comparison of three different vaccine supply chains and how they performed in terms of responsiveness. The responsiveness aggregate indices matrix in Table 11 and the partial performance measures matrix in Table 10 can provide some details on the parts of the vaccine development, manufacturing, and supply chain that have a significant role in being able to respond to situations like a pandemic. In general, when looking at the aggregate indices, the higher a number is the more responsive that supply chain can be. The following sections will evaluate the results in to investigate the two analysis objectives.

Pfizer and BioNTech Partnership Responsiveness

Pfizer and BioNTech partnered to create the first mRNA vaccine that had received emergency use authorization and then first to get full FDA approval. The aggregate indices matrix can be used to evaluate how this partnership affected their ability to be responsive. In this analysis only the aggregate indices of the BioNTech by themselves as a company and the Pfizer and BioNTech partnership are relevant to the objective.

Starting with the product details category, both companies ended up making the same vaccine with the same technology there is no difference in their responsiveness values. The company category is where the scores change and can give some details into how the partnership may have affected their ability to be the most responsive. Company resources and size is a major factor when it comes to being able to produce enough product to meet the high demand of a vaccine that is used to fight a pandemic. BioNTech is a smaller company in comparison to a large company like Pfizer and thus it would be more difficult for them to be able to be able to fulfill the high demand. In the aggregate indices BioNTech

on their own have the lowest score in the company category at 0.1875. When BioNTech partners with Pfizer the company score increases to 0.3125. When looking at the partial performance measures, the specific resources that stand out as impacting the total responsiveness is the equipment, facilities, and materials resources. This shows that when Pfizer brings their company resources to the partnership, they can be much more responsive at creating a vaccine. When looking at the manufacturing and supply chain categories there is a similar story in that when Pfizer brings their size to these various categories, they can be more responsive.

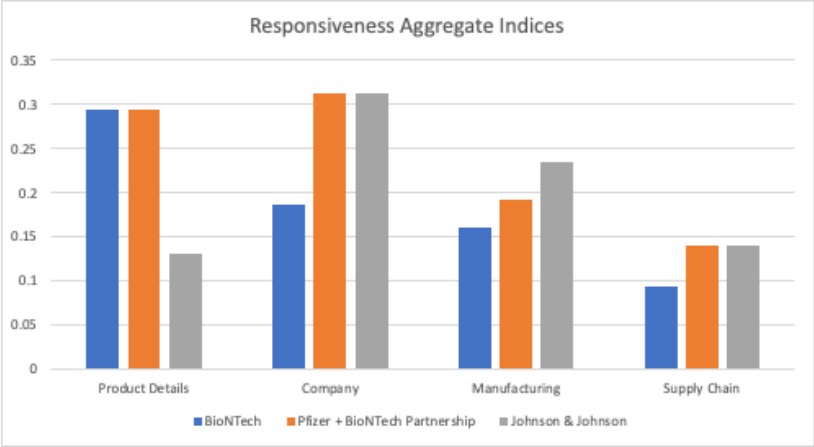

Figure 7 : Chart of Aggregate Indices

Type of Vaccines on Responsiveness

To meet the next analysis objective of evaluating the type of vaccine effect on responsiveness, the Pfizer and BioNTech partnership indices and the Johnson and Johnson indices can be looked at. The product details category that Pfizer and BioNTech have a score of 0.29375 and Johnson and Johnson has a score of 0.13058. This difference is large compared to the other categories. Because of this it is determined that the type of vaccine can play a huge role in how quickly a vaccine can be brought to market to respond to a pandemic. This aligns with some of the advantages to mRNA vaccines that Rosa et al. describe in their paper on mRNA vaccine manufacturing in that they can be developed in vitro and are created for specific antigens (Rosa, Prazeres, Azevedo, & Marques, 2021). Lemmens et al. describe that a challenge for the vaccine industry is the development of

rapid response vaccines supply chains for the sake of pandemics or bioterrorism. Hopefully with the experience of the SARS-CoV-2 pandemic and further research of different types of vaccines such as mRNA vaccines a rapid response supply chain can be achieved.

Overall Responsiveness

By summing the aggregate responsiveness indices for each company, the total responsiveness score can be achieved. This score shows the overall performance of each of the supply chains that are being analyzed. The sum of these scores for BioNTech, the Pfizer and BioNTech partnership, and Johnson and Johnson are 0.736, 0.939, and 0.818 respectively. These sums of aggregate indices are shown in Figure 8. This figure shows that Pfizer and BioNTech partnership is the most responsive. This makes sense as they were the first to receive EUA and subsequently full FDA approval. The next most responsive company was Johnson and Johnson, and this shows that despite them selecting a vaccine type that takes longer to develop their company resources can make them more responsive than that of BioNTech had they developed the SARS-CoV-2 vaccine without the partnership of Pfizer.

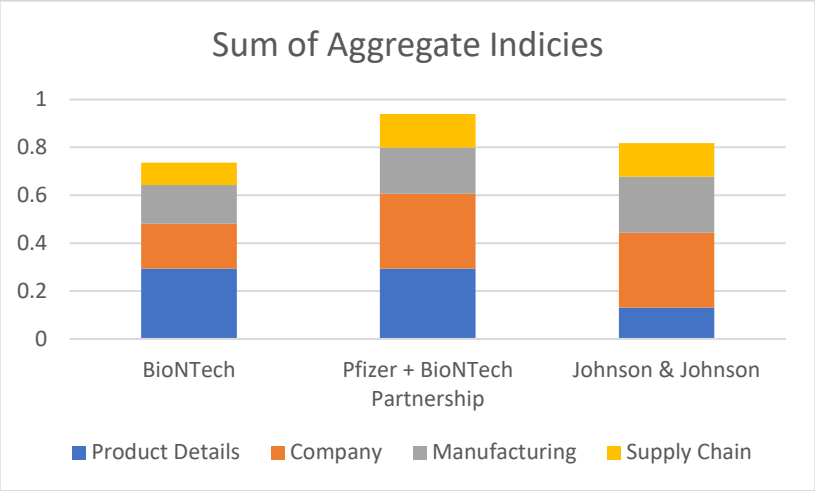

Figure 8 : Sum of Aggregate Indices

Conclusions

This thesis began with four objectives. The first two were associated with the development of a responsiveness evaluation model that would allow companies and researchers a way to quantify their responsiveness performance. The first objective was to determine what factors affect a vaccine company's ability to be responsive in developing a vaccine to meet an unexpected high demand within a desired customer wait time. This objective was met by developing the responsiveness performance measures for the vaccine industry. These measures can be adjusted, and others can be developed based on what responsiveness information is trying to be obtained. The second objective was to use these factors to develop an evaluation model to quantify a company's performance in terms of responsiveness. This objective was also successful in adapting Soni and Kodali's performance value analysis methods along with the responsiveness performance measures that were developed.

The next two objectives were about how to set up the model to evaluate the responsiveness of the various companies that developed vaccines for the SARS-CoV-2 pandemic. The first of these objectives was to evaluate the how the type of vaccine affects the responsiveness

of a company. To do this an analysis on the performance of the Pfizer-BioNTech mRNA vaccine and the Johnson and Johnson viral vector vaccine was performed. These two were chosen because many of the performance measures were similar for each of these companies except for the difference in product details that are associated with the difference in type of vaccine. The conclusion of this analysis was that they type of vaccine can play a difference in how responsive a company can be when developing a vaccine. This is shown by the Pfizer-BioNTech vaccine being scored higher than Johnson and Johnson in the product details category as well as the overall responsiveness score. The last objective was to evaluate how intercompany partnerships can affect the responsiveness of the vaccine supply chain. To do this a comparison was done on just BioNTech and their ability to develop the SARS-CoV-2 vaccine on their own versus their ability to develop the vaccine when they partnered with Pfizer. This analysis showed that there is also a significant impact on resources, manufacturing capabilities, and established supply chains when it comes to being able to be responsive in the vaccine industry. This is shown in that in the company, manufacturing, and supply chain categories, the addition of Pfizer as a partner was beneficial to both companies in being able to be responsive and develop a vaccine quickly.

Limitations

The creation of the responsiveness analysis model using the PVA method was successful in that various supply chains can be evaluated based on our responsiveness measures. Based on how the measures are organized into categories or how we define our alternative supply chains we can evaluate different areas of the vaccine industry to see where it can be improved in terms of responsiveness. The main limitation of this study is that real world company data could not be readily accessed and analyzed to evaluate an actual supply chain. This limitation means that sometimes educated guesses have to be made and use company reports to be able to test the PVA method. Working with an actual pharmaceutical company to evaluate their responsiveness would help show the effectiveness of the model in improving the responsiveness of the vaccine industry.

Directions for Further Research

Within the vaccine industry further research can be done in this area by continuing to evaluate the performance measures defined in this thesis to see their actual impact on responsiveness. This would help refine the model to be able to more accurately be able to assess the responsiveness of a company and their supply chains. This model can then be used to study what a rapid response vaccine supply chain looks like as Lemmens et al. describe. Working with a company to apply this model and method to their supply chain would also be a next step in developing this analysis method.

Finally, responsiveness does not just apply to the vaccine industry. This model and analysis can be applied and adjusted for various industries by developing their own performance measures and metrics specific to that industry.

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