How Distrust in the Pharmaceutical & Healthcare Industry May Cause Complications Implementing a Pulmonary Tuberculosis Vaccine

(STS Topic)

Design of Manufacturing Plant for Keytuda Using Perfusion Technology

(Technical Topic)

A Thesis Prospectus
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By

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Technical Prospectus

The cancer immunotherapy drug Keytruda, also known as pembrolizumab, is a checkpoint inhibitor monoclonal antibody (mAb) manufactured by Merck. Cancer is the second leading cause of death in the U.S., with the number of cancer cases expected to rise from 14.1 million in 2012 to 23.6 million in 2030 (National Cancer Institute, 2015). Associated with this increase in disease rates is a shift in technology within the pharmaceutical industry in hopes of addressing these disease rates. Antibody-based drugs, specifically, have risen as the fastest growing class of protein therapeutics due to their increased efficacy, decreased immunogenicity, improved deliverability, and decreased potential to adversely affect normal biological processes compared to standard chemotherapy treatments(Awwad & Angkawinitwong, 2018).

Keytruda works by blocking the PD-1 pathway. By doing so, immunogenic T-cells can locate cancer cells and induce a natural immune response (Merck & Co., 2019). This novel mechanism of action, coupled with low side effects when compared to chemotherapy, makes Keytruda an extremely promising drug in the fight against many types of cancer. Although Keytruda was initially used to treat lung cancer, it has and is continuing to receive increased market approvals for oncology indications. Due to increasing global demand, Merck announced that it will build a $300 million Keytruda manufacturing facility in Dublin, Ireland. The facility will begin manufacturing operations in 2022 (The Irish Times, 2018).

The current process of mAb production includes culturing mammalian cells that produce the recombinant mAb protein in a large steel batch reactor. This is followed by several unit operations to separate the desired product from the fermentation media (Gillepsie, et al., 2014). These batch steel reactors are large, expensive to operate, and have low product yields. They also require extensive cleaning protocols involving potent and abrasive chemicals, which are necessary to appropriately sterilize the reactor (W. Runstadler, 1992). A lack of the aforementioned changes to process design can contribute to high production costs, decrease the ability of a single facility to produce different drug products, and cause additional conflicts with environmental regulations due to the potency of the reactor cleaning chemicals.

We plan to design the new Merck Keytruda production facility with perfusion reactors and single-use bags. Incorporating single-use reactor bags will decrease the need for extensive cleaning protocols, save time, reduce employment costs, improve compliance with environmental regulations, improve the modularity of the manufacturing facility, and ensure product purity between batches (Jacquemart, et al., 2016). Using a perfusion reactor will allow continuous production of Keytruda, rather than the production of the drug in batches. Perfusion bioreactors culture cells over longer periods by continuously feeding and removing media while keeping cells in culture (Bielser, Wolf, Souquet, Broly, & Morbidelli, 2018). This continuous production will increase product yields and subsequently decrease production costs. Perfusion reactors also traditionally require fewer operators, further decreasing production costs (W. Runstadler, 1992).

Therefore, we propose the design of a Keytruda manufacturing plant that uses the aforementioned manufacturing strategies. This process will start with the fermentation of Chinese hamster ovary (CHO) cells with incorporated recombinant DNA for Keytruda. These cells will be grown in serum-free CHO media in a stirred 10,000-liter perfusion reactor. The cell culture broth will then be clarified through centrifugation and continuously fed into downstream purification unit operations of protein A chromatography, anion exchange chromatography, cation exchange chromatography, and diafiltration (see *Figure 1*). A water-for-injection purification system will also be designed for the facility in order to provide sterile water for each production step.

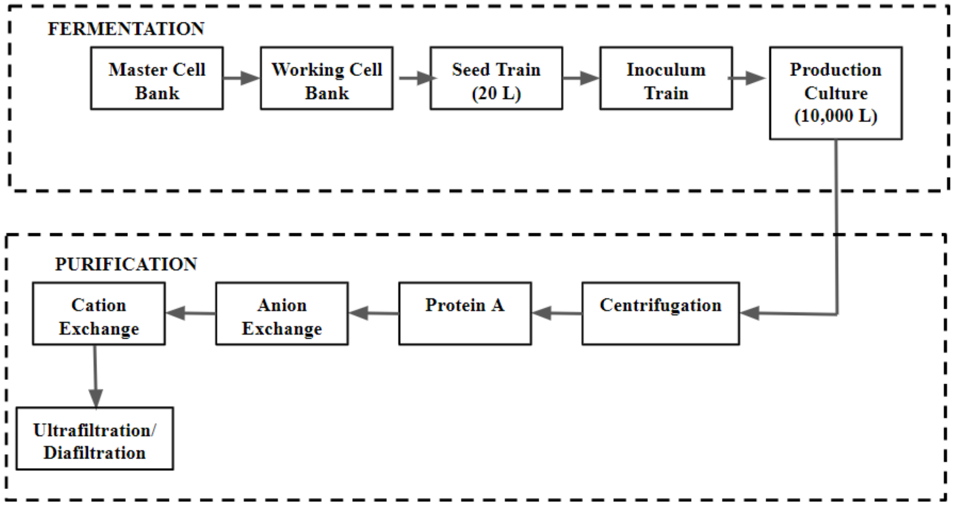

Figure 1: Generalized process flow diagram for the production of monoclonal antibody. Adapted from Petrides, Siletti, Carmichael, & Koulouris, (2014).

Aspen Plus V11 and MATLAB will be used to model the several unit operations involved in Keytruda production while implementing theories of bioseparations, kinetics, transport phenomena, and thermodynamics. Our team will need to estimate projected Keytruda demands in order to calculate how much drug should be produced to appropriately size equipment. We will produce a Design Basis Memorandum in Fall 2019 and complete the technical design in Spring 2020.

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STS Prospectus

A. Introduction

The pharmaceutical industry has been the subject of growing American public distrust in recent years with the Americans polling at 58% overall negative opinion towards the industry with only 27% reporting a positive overall opinion, worst among industries listed in the gallop pole.[1] The topic I have selected for my STS research paper is how public distrust could affect proper utilization of vaccine technology. I will specifically investigate how distrust in the pharmaceutical and healthcare industry inhibit the global success of a future tuberculosis vaccine. Successful roll out of new drugs requires a collaboration of supporting factors and as a result the framework I have chosen to apply to this is actor-network theory. My STS paper will construct the complicated descriptive network which is exists to distribute and utilize the new vaccine technology then analyze which actors have connections at risk of erosion if distrust among the public could continue to grow. A normative network will also be defined to show how in addition to strengthening current network connections, additional actors should be brought in to ensure and advance global vaccine success. After the networks and actors of note, are examined potential methods for strengthening and growing the network will be proposed based on the causes of both network erosion and actor exclusion ANT has identified. The paper will establish that key standard of success will be achieving high vaccination rates globally. The objective will be to show how the availability of this vaccine in areas of low socioeconomic status will prove be a significant challenge. Another threat of interest to tuberculosis vaccine success is rising “vaccine hesitation” due to misinformation causing vaccination rates among those with availability to fall. The overcoming these obstacles could prove too difficult if the relationship between the public and “big pharma” continues to worsen and causes support for global initiatives to falter and voluntary opt out to rise.

Though this framework will be applied to the potential tuberculosis vaccine, it has some connection mildly to my technical report. The technical report will describe my capstone project: designing a pharmaceutical manufacturing facility to produce Keytruda, Merck’s blockbuster checkpoint inhibitor drug for treating lung cancer. Manufactures of pharmaceuticals are one of the actors in the network for rolling out the drug. The design choices I will make include the location, production rates, and economics will provide insight into how manufactures of a tuberculosis vaccine can affect the other actors in the network.

Immunization has been used to combat disease dating back to 17th century China when venomous concoctions were consumed by monks to prevent the effects of snake bites. [2] Modern vaccines as a method for immunization began in the 18th century when Edward Jenner, whose wife coincidentally had recently died of tuberculosis, tested a hypothesis that the puss of cows encountered by milk maiden contained a non-harmful version of the small pox disease by injecting Jenner’s gardener’s son in both arms. [3] The immunization to small pox was successful culminating in the first vaccination and the scientific basis for vaccinology. [4] Since then vaccines have become the wildest used method of immunology worldwide. Over the past two century vaccines have been employed globally to completely eradicate smallpox and rinderpest. Polio has diminished to less than 500 new cases per year only in limited middle eastern regions such as

Afghanistan, Nigeria and Pakistan. [5] The united states, has nearly eradicated tetanus and bacterial influenza. Though subject to media coverage due to its role in sparking the “Anti-vaxxer” movement, the MRR vaccine has still been considered effective in combating measles mumps and rubella. [6] Despite the amazing technological innovation that vaccines, the effectiveness in treating widespread disease is subject to challenges that go beyond lab development of the antibody formula that goes into the syringe. These additional challenges which have frequently reappeared and have often dominated vaccine policies take the form of funding mechanisms, streamlined manufacturing and safety concerns, and deep-seated public fears of inoculating agents.[7]

A. Success in Vaccines: Community Immunity

A metric of success for a new vaccine is how effective it is at creating a global community immunity to the disease it immunizes for. This is the only way a vaccine that completely protects against contraction of a disease is useless if only a small percent of the population utilizes it. Every new user? of a vaccine not only immunizes themselves but eliminates their potential for becoming a disease incubator and distributor. Disease spread is a nonlinear phenomenon and by keeping the potential hosts small, vaccines prevent outbreaks from taking hold. [8] Furthermore, community immunity is especially important any people with sever allergies or compromised immune system who cannot be vaccinated due to their preexisting conditions. [9] Additionally, it is insufficient for only a local community immunity to be established in the 21st century. Zones where diseases have been eradicated, such as many first world countries, still must participate in vaccination. The international travel that results from the many other global networks give ample opportunity for infection to spread between zones of various vaccination levels. Between 2001 and 2005, polio cases across Africa and Asia spiked due to the decreased vaccination rates in Nigeria.[10] Polio virus unfortunately became one of the most impactful exports of the country. The only way to render a vaccine obsolete is to achieve a total global eradication of a diseases.

The importance of the immunization increases for diseases which are highly contagious. Pathogens spread from those infected with these highly infectious diseases can remain airborne for hours after the infected individual leaves a room or dwelling. [11] The highly contagious nature of diseases like measles, vaccination rates of 96% to 99% are necessary to preserve herd immunity and prevent future outbreaks.[12] This extends to tuberculosis which is currently estimated to have infected 1.8 billion people, almost a fourth of the world's population.[1] Once the technology is successful, the most critical aspects to driving this community immunity are financing global distribution and participation.

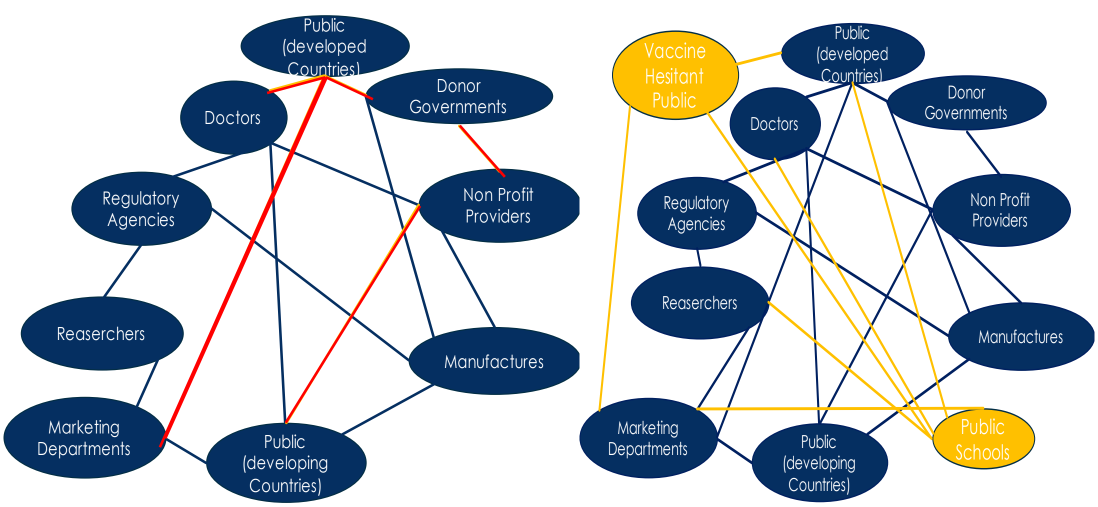

Figure 1 – Descriptive (left) and Normative (right) Networks Depicting the Actors Involved with Vaccine Success & Effectiveness along with connections illustrating interactions. Blue Connections Indicate Normal Interactions while Red Connections indicate Eroding Interactions. Yellow Connections and Actors Indicate Actors and Interactions which need to be Brought into the Normative Network

Its estimated that in low to mid income countries, over 10 million children fail to reach the age of 5. [10] A large deaths associated with preventable childhood illness which could be prevented by vaccination. These areas where this is the most prominent are Central Africa and South Asia. In the average cost of vaccines in the United states is 136$. This cost in African countries is cut down to 39$ in the countries which receive the most support. [13] However, in these poor countries such as Liberia or The Central African Republic, the gross national income per capita is $710 and $730 respectively. [14] This low income presents obvious economic barriers which result in low availability of vaccines in these areas. These areas are also the candidates for the highest demands of a Tuberculosis vaccine with South-East Asia accounting for 44% of new cases followed by Africa at 24%.[15]portion of these

Organizations such as the World Health Organization and the United Nations are the main drivers which support programs which provide vaccines to those who could not afford them otherwise. The largest of these programs is the Global Alliance for Vaccines and Immunizations (GAVI) which is a private public partnership that works to fund and distribute vaccines in areas which cannot afford them. The funding mechanisms for GAVI are three-fold. GAVI is a beneficiary of the International Finance Facility for Immunization (IFFIm) which leverages for long term financial donations made by economically strong donor countries in the form of "vaccine bonds" which then are sold to generate capital in the short term.[16] The second mechanism is the Advance Market Commitment (AMC) which takes upfront promises from donor countries to purchase future vaccines that, if developed, would be needed only in areas that could not afford them thus guaranteeing a market and incentivizing pharmaceutics companies. [17] Finally, certain countries decide to donate directly in the form of immediate grants to nonprofit vaccine providers. The biggest donors to these programs are well developed countries such as the UK, US, Norway, Germany, & Canada. US donations along amount to 12.1 billion USD supporting the Global Alliance for vaccines and Immunizations. The US has restrictions on mutli-year commitments which prevent pledges of donor bonds and donate directly to GAVI. This means that the US aid is in the form of annual grants and as a result is subjected to yearly changes in policy and volatility of public support. The US Congressional House of Representatives, the most frequently elected body, is the governmental body which approves such funding.[17] If growing disproval of the pharmaceutics industry continuous it could pose a risk to voter approval of appropriating millions of tax payer dollars for purchasing vaccines from these companies for foreign aid. This would fundamentally erode a key interaction in the current vaccine network between developed donor countries and nonprofit organizations. Since The nature of this relationship directly ties the availability of vaccines in low income areas to public funding, it indirectly connects availability of vaccines in low income areas of the world to public (voter) perception of pharmaceutics companies in the more affluent countries.

c. Voluntary Enrollment

The widely reported on "Anti-Vaxxer" movement has caused the world health organization to list "vaccine hesitation" as a top ten threats to global health. The Anti-Vaxxers are a group of people who choose to not get vaccinated or vaccinate their children despite having the means and access to. The cause of the modern movement stems from proposed link between the measles vaccine and childhood autism. [18] In 1998, a British doctor Andrew Wakefield first made the connection between the measles, muphs, and rubella (MRR) vaccine and bowel disease (autism). These findings have been publically condemned and retracted by numerous scientific organizations. The General Medical Council of the UK has cited numerous conflicts of interest. This was followed by the British Medical Journal publishing findings that Wakefield had committed scientific fraud. Further controversy has more recently arose with regarding the use of a mercury-containing preservative called thimerosal. The Internal Organization for Medicine had published findings that conclude “the evidence favors rejection of a causal relationship between thimerosal–containing vaccines and autism.” [18]

The anti-vaxxer movement seems to grow in the face of logical decision making despite the availably of evidence discrediting it. [19] Almost 1 in 10 Americans believe that vaccines are unsafe. [19] Supporters of the movement reject this Information in favor of misinformation citing financial motives of “big pharma” to discredit accepted science. Instead they turn to the unregulated and non-reviewed information spewed on social media likely because it comes from more trusted figures such as Jenny McCarthy, who propel anti-vaxxer ideology to their followings. Additionally, scientific rejections may result from self-suggestion occurring on social media when members of the anti-vaxxer community barricade themselves in echo chambers providing self-validation of ideas and hiding the ability to see how in the minority they are.[19] The hotspots for anti-vaxxers in the United States appear to be on the west coast, especially in affluent communities. The results of vaccine hesitation can best be illustrated in the 2014-2015 Disney measles outbreak in Anaheim California. Approximately 125 cases of measles resulted from an outbreak in the area caused by an estimated 50% MRR vaccination rate. [20] if ideology were to spread in this new era of rejecting science in favor alternative facts it may lead to higher opt out rates nationwide.

D. Network Erosion Prevention and New Member Recruitment

In order to mitigate the further erosion of the network as it stands, there are avenues which can be explored which would combat the distrust of pharmaceutics science and healthcare industry as a whole. The important connections in the network either at risk are highlighted in figure 1. This public in developed countries is at the core of network erosion since there distrust can lead to both drop in voluntary rates and removal of support for public funding of global initiatives. One potential way to strengthen their position and prevent portions of the population from leaving is to address misinformation spread on social media. As many as half of all new parents with children under the age of 12 have been exposed to misinformation on social media regarding the safety of vaccines. [20] Most of these incidents involve word play and subtle nuances not understood by the general public to make and support unsubstantiated statements which contradict sound science and cast doubt in public perception. An article from Harvard's school of public health claims that these tactics include using correlations as causation or using uncontrolled personal experiences as equivalent to well-designed observational studies or experimentations.[22] Since autism is generally discovered around the same time children undergoes immunization, tactics can have powerful impact on individual members of the public when dealing with stressful topics such as the health of their kids. Heidi J. Larson, a professor of risk and decision science at the London School of Hygiene & Tropical Medicine, predicts "the next major outbreak —will not be due to a lack of preventive technologies. Instead, emotional contagion, digitally enabled, could erode trust in vaccines so much as to render them moot. The deluge of conflicting information, misinformation and manipulated information on social media should be recognized as a global public-health threat." [23] Censoring post which can be proven without a doubt to be providing untrue information regarding major public health issues could be effect but opens up a slew of ethical questions. Alternatively promoting posts touting science meant to set the record straight may prove ineffective if it gets publicly rejected based on distrust of pro pharma sources. In addition to ANT analysis, I will investigate the efficacy of different methods on curbing the spread of misinformation on social media in order to prevent growth of vaccine hesitation public support of as part of my STS thesis.

For bringing in the actors not currently apart of the descriptive network to produce a high functioning normative network, actors such as public-school systems, researchers and pharmaceutics marketing departments must establish connections with anti-vaxxers and vaccine hesitant in order to not only stop their growth but change their opinion. Doing this requires mending the deep-seated distrust they have with pharmaceutical company's. The mechanism for this is marketing from pharmaceutical companies on the various positive endeavors the companies participate in. In 2017 pharmaceutical companies gave 3.25% of total revenue to charity. This amounts to billions of dollars aiding various philanthropic ventures worldwide. A quote from the executive VP for PRA Health Sciences, Michael Brooks says "Pharma could definitely do a better job promoting its philanthropic endeavors…Many people don't know that drug companies are among the most generous corporate donors and that much of that giving is in product donations."[24] Better exposer of this might be able to persuade certain people away from the "evil empire" view they hold of these companies. When this is combined with government education programs both in the form of public school education, perhaps in biology class, and in advertisement campaigns could bring potions anti-vaxxers and already vaccine hesitant population into the network thus strengthening voluntary enrollment and funding support for global vaccine providing programs.

E. Conclusion

The two biggest challenges preventing community immunity globally is the lack of immunization due to either economic inability to obtain the vaccines or “vaccine hesitation” caused by fear and misinformation.[3] The distrust in the pharmaceutical and healthcare industry is what opens the door for rejection of science causing the inability to cube the anti-vaxxer efforts. The result of this could lead to lack of public support for global initiatives which provide vaccines to impoverished areas of need. The ability to generate high voluntary enrollment and public support global funding for a Tuberculosis vaccine is critical to achieving a community immunity. The public of affluent countries therefore occupy multiple roles in the network involving acceptance of the new vaccine and influence over public governments which act as financers. With Tuberculosis being one of the most prominent diseases on the planet, we cannot afford to overlook the rising effects of growing distrust has on preventing anti vaccination efforts from inhibiting or slowing global financing and distribution networks.

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