Prospectus

Design of a Pembrolizumab Manufacturing Plant in Ireland Using Continuous Bioprocess Technology and Single-Use Bioreactors
(Technical Topic)

Actor Network Theory of Purdue Pharma in the Opioid Crisis
(STS Topic)

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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Sociotechnical Problem

Cancer is a life-threatening illness that has invaded and stolen the lives of billions of people. It has manifested roots deep within society, with profound impacts on the patient, friends, families, economies, and the community as a whole. Cancer patients themselves must endure a lifestyle change, as their social, physical, emotional, and financial stabilities are greatly compromised. In 2018, 1,735,350 new cases of cancer were diagnosed in the US, and 609,640 lives were taken from the disease. This disease has been a bane to this nation, with 2017 US cancer expenditures of $147.3 billion, which is only expected to increase as prevalence increases and more expensive treatments are adopted (National Cancer Institute, 2018). The word alone strikes a chord of fear in most people, as many cancer survival rates are grim.

In order to address this problem, I am designing a pharmaceutical manufacturing facility for production of the cancer immunotherapy drug Keytruda. This process involves defining several unit operations, starting from cell culture, until the drug is purified and ready for injection. As Keytruda gets market approvals for oncology indications, it has the potential to treat an increasing variety of cancers.

However, designing a pharmaceutical plant alone is not a comprehensive solution to treating cancer. Pharmaceutical engineers are typically only concerned with product purity and fail to consider that the success of the drug is affected by several downstream actors, which can impact how the drug is marketed, administered, and used. If drug manufacturers fail to consider the broader network surrounding a cancer drug, they may not be successful in treating cancer, as there may be some unforeseen negative impacts. Though Keytruda was developed with intentions to treat cancer, it is important that the solution to this problem does not cause additional consequences, such as how opioids were developed with intentions to alleviate severe

pain, but now fuel addiction. Therefore, I am interested in examining how the opioid crisis has been fostered by the complex power dynamics between actors of the opioid network. Studying a network like this will allow further understanding of how to effectively market and distribute Keytruda in a safe and effective manner.

In order to treat cancer holistically, both the technical and social aspects of the problem must be addressed. Below I outline a technical process for designing a cancer immunotherapy drug production facility, including all of the unit operations involved in the manufacturing of the pharmaceutical drug. I also use Michel Callon's actor-network theory to analyze how Purdue Pharma built a network that ultimately resulted in the nation-wide opioid crisis.

Technical Problem[1]

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

[1] This section was written collaboratively with Brian Abt, Clayton Burruss, Revathi Mohan, and Noah Rushin in order to comply with direct and specific requirements of my technical advisor, Eric Anderson.

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.

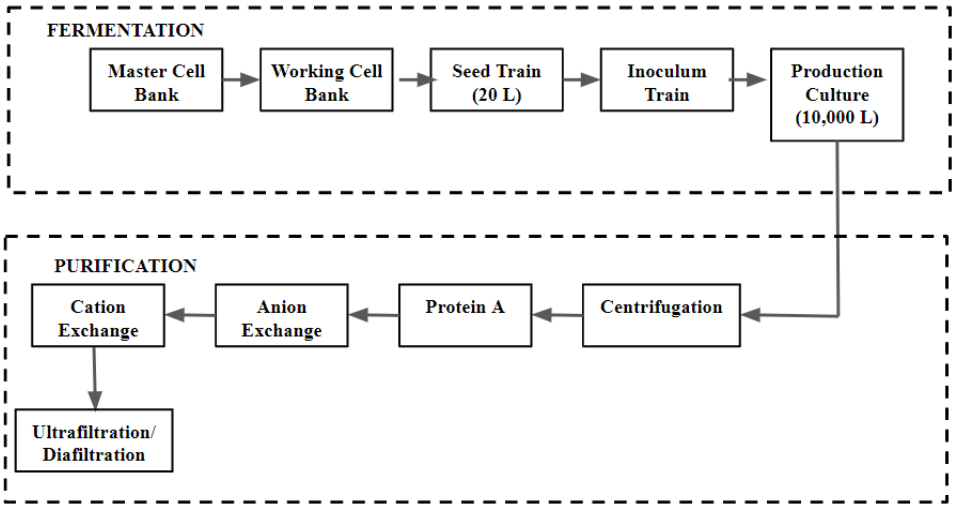

Figure 1: Generalized process flow diagram for the production of monoclonal antibody. Adapted from Petrides, Siletti, Carmichael, & Koulouris, (2014).

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.

STS Problem

The opioid crisis has taken more than 400,000 lives from 1999-2017, with estimated expenses to have exceeded $1 trillion from 2001-2017 (Rhyan, 2017), and additional predicted cost of $500 billion by 2020 (National Academy of Medicine, 2019). Since 1996, Purdue Pharma, owned privately by the Sackler family, has earned more than $36 billion in revenue from the sale of their popular opioid drug OxyContin (Ofgang, 2016). Opioids are an extremely potent and addictive class of drugs including morphine and heroin, with popular brand-names such as OxyContin, Vicodin, and Percocet. Within the medical field, they are used to treat severe pain due to their ability to block the pain signals between the brain and the body. However, opioids have also been used to make people feel relaxed, happy, or "high," thus making the drug highly addictive (Johns Hopkins Medicine, 2018).

Since the 1990s, doctors have been very cognizant of the high risks associated with prescribing opioids, and prior to the 1990s, they only prescribed them sparingly to cancer patients with acute, chronic pain. When OxyContin was approved by the FDA in 1996, Purdue Pharma flooded the medical field with claims that OxyContin's time-release mechanism made it less addictive and suitable for more moderate pain treatments, toting it as the "pot of gold" waiting "over the rainbow" (Ofgang, 2016). Doctors heard the same information from pain specialists, addiction specialists, professional societies, and hospitals, all of which were paid by Purdue in a massive marketing campaign. No one prior to Purdue had marketed a high strength

narcotic in the way Purdue was, and these efforts were proven successful when the Sackler family, dubbed the "OxyContin Clan," was named to the 2015 Forbes' list of 20 richest US families with an estimated net worth of $14 billion (Ofgang, 2016).

Purdue Pharma is currently being accused in over 2600 federal and state lawsuits for misleading doctors and patients by overstating the benefits and downplaying the glaring risks of OxyContin (Walsh, 2019). Courtrooms nationwide are pointing to Purdue for the causation and continuous exacerbation of the opioid crisis, as its aggressive marketing techniques led the movement to change the medical community's view on the prescription of opioids (Barstein, 2019). However, these lawsuits overlook that there were several other groups that have assisted Purdue Pharma in the marketing and distribution of opioids, such as the FDA, and the healthcare system itself. If we continue to believe that Purdue Pharma alone was responsible for the opioid crisis, we may fail to recognize the other actors that have contributed significantly to the crisis throughout the years. Assigning blame only to Purdue will construct an incomplete picture of the opioid crisis, and those looking to resolve it will have an inadequate understanding of the how the problem truly manifested. In this research paper, I will use actor-network theory to emphasize how Purdue Pharma was only able to successfully foster a nefarious network of opioid addiction by operating in conjunction with several groups, such as doctors and medical organizations. By recognizing that the opioid crisis was a result of several groups working together, we will be able to form a more holistic view of the opioid crisis, and thus gain a better understanding of the factors that have allowed for opioid addiction to run rampant. Actor-network theory is a conceptual framework examining the power dynamics and mechanisms between the human and non-human actors assembled by a network-builder to accomplish a goal. By assigning equal agency to both human and non-human actors, actor-network theory is able to

fully understand the successes, failures, and vulnerabilities of a heterogenous network (Callon, 1987). In this paper, I will be exploring the Purdue Pharma network involving actors such as OxyContin, doctors, and medical organizations, and how the network as a whole was able to successfully manifest and profit off of nation-wide addiction.

Conclusion

In this paper, the technical and social solutions come together to address and create a comprehensive treatment of cancer. The technical solution addresses the complex manufacturing design of the cancer immunotherapy drug Keytruda, which is important for production costs and final product quality. The STS research paper will provide further insight into how technologies, originally designed as a solution to one problem, may often have unanticipated consequences that drastically outweigh the benefits. This analysis will specifically focus on how Purdue Pharma built a network with a goal to foster the national opioid addiction, and how the actors within this network have allowed Purdue Pharma to be successful in its goal.

The results of both the technical report and the STS research paper will work together to address the broader sociotechnical issue of providing a more affordable, accessible, and less potent cancer treatment. By understanding the technical details of cancer drug production in conjunction with understanding the power dynamics of the drug within a network, pharmaceutical engineers can better ensure that they are creating a well-rounded cancer treatment, and we can get one step closer to defeating this invasive disease.

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