Design of an mRNA Vaccine Manufacturing Platform to Target *M. Tuberculosis*

Analyzing the Effect of Patents on Innovation and Drug Accessibility Within the Pharmaceutical Industry: A Case Study on Bedaquiline

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

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Introduction

Vaccines have evolved significantly since their introduction in 1796, yet there is an increasing demand for large-scale production and novel vaccine development (Wang et al., 2021). mRNA vaccines hold potential for fighting both cancer and infectious diseases, offering advantages in safety, efficacy, flexibility, and commercial scalability compared to traditional vaccines (Schlake et al., 2012). Challenges such as instability, high raw material costs, and inefficient delivery systems persist, so it is critical to improve upon current delivery mechanisms, specifically lipid nanoparticles (LNPs) (Matarazzo & Bettencourt, 2023). LNPs encapsulate mRNA via rapid mixing, protecting it from enzymatic degradation and facilitating its release into the cytoplasm for antigen synthesis (Hou et al., 2021). Because any protein can be encoded and expressed by mRNA, this process allows for the manufacturing of vaccines targeting various diseases, including cancers, influenza, SARS-CoV-2, HIV, and tuberculosis (TB) (Schlake et al., 2012). TB is of particular interest given its status as a leading cause of death in low- and middle-income countries and lack of an effective vaccine. mRNA technology simplifies the development of vaccines against complex infectious diseases like TB, which rely on T cells for protection (Matarazzo & Bettencourt, 2023). Our work aims to replicate and optimize the mRNA vaccine production process with a particular focus on the LNP delivery system and rapid mixing technique. Using TB as a case study, we seek to address the complexities of bacterial infections and employ mRNA technology to develop more efficacious vaccines, aligning with recent technological innovations and global public health priorities.

Technical Project Proposal

Our process will be designed based on the research of Daniel et al. (Figure 1). The research identifies three main phases of RNA vaccine manufacturing which include the manufacturing of the RNA active substance, formulating and purification of the lipid nanoparticles, and the final fill-to-finish. Our design will focus exclusively on the mRNA and lipid nanoparticle synthesis and purification, ending at the sterile filtration step identified in Figure 1. The feeds to our process will include all necessary nucleotides, enzymes, and lipids to synthesize mRNA and lipid nanoparticles at an industrial scale. Our finished product will be a purified and sterilized suspension of lipid nanoparticles formulated with a desired mRNA sequence.

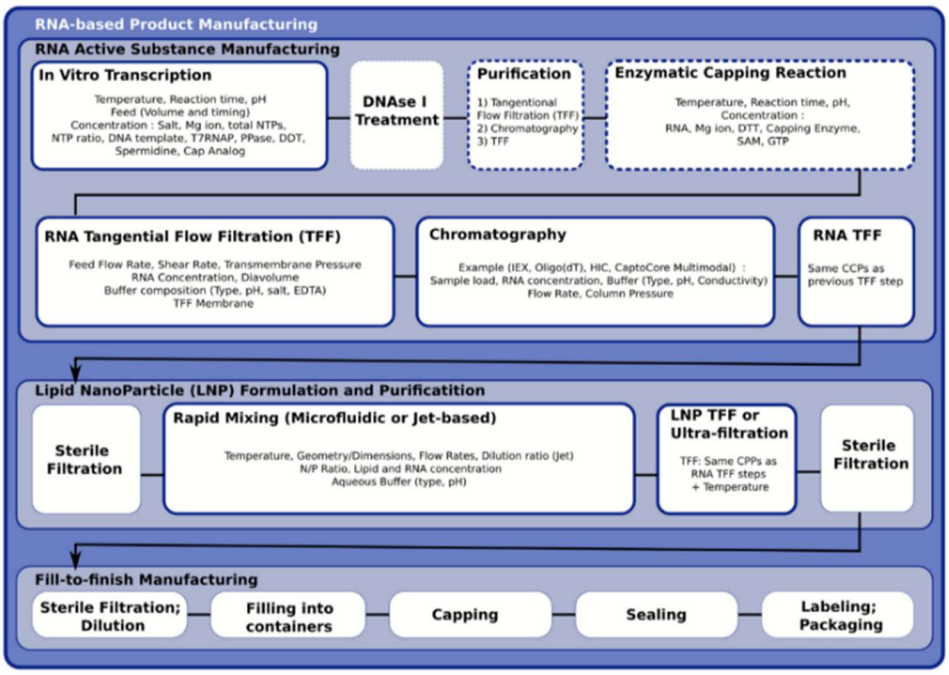

Figure 1. Process Flow Diagram of the mRNA Vaccine Manufacturing Process (Daniel et al, 2023)

Our mRNA vaccine manufacturing process will involve several unit operations. A batch-fed bioreactor will perform both the in vitro transcription and enzymatic steps (DNA degradation and capping) of the process. For purification, we will employ a combination of chromatography

methods, including affinity resin-based, anion-exchange, and hydrophobic interaction chromatography. These methods will purify full-length mRNA from impurities such as DNA fragments, enzymes, unreacted nucleoside triphosphates, unreacted caps, incomplete mRNA sequences, etc. (BioPhorum, 2023).

Tangential-flow filtration (TFF) will be used with chromatography to purify and concentrate mRNA after transcription, enzymatic capping, and lipid nanoparticle (LNP) formation, before fill-to-finish. Sterile filtration will be implemented in three stages: before LNP formation, after LNP formation, and before filling. In all, these processes will ensure that our final mRNA product meets quality standards and is safe for patients.

For encapsulating the mRNA product, we will use either jet-based mixing or microfluidic mixing to form the LNPs. The final choice between these two methods will be determined at a later stage of development.

Our design for developing an mRNA manufacturing process will be carried out over two semesters. By the end of the fall semester, we aim to clearly define the scope and scale of the process. The project will culminate in a final report that includes detailed design calculations and an economic analysis.

The work will be divided by the process stages. Two members will work on designing the batch-fed process scale-up for the mRNA production. One member will design a scale-up for the purification of the mRNA product. The final two members will work on the lipid nanoparticle sections, designing the LNP formation and the final encapsulation stage.

Regarding computation tools and software, we will use Aspen Plus to model applicable sections of the process. For more detailed calculations, data analysis and process modeling that

cannot be done in Aspen, we will use MATLAB or Python. We may also explore alternative software options, such as COMSOL, for specific simulations involving fluid dynamics and heat transfer.

To gather necessary design data, we will seek to understand current mRNA manufacturing processes and review papers and articles on lab-scale operations. We also plan to consult experts, such as Dr. Mike King, who have industry experience, to gain insight into challenges and opportunities specific to our process. Essential data will include, but are not limited to:

- mRNA synthesis "recipes" – the number of base pairs, enzyme concentrations, etc. based on sequence length
- LNP formulation details – lipid combinations and ratios for achieving desired particle size and properties
- Dosing and market size information
- Information on potential solvents and adjuvants, including thermodynamic properties

Our approach will emphasize a balance between individual responsibility and team collaboration. By leveraging a wide range of computation tools and reliable data sources, we aim to develop a safe, feasible mRNA therapeutic manufacturing process.

STS Project Proposal

In 2023, tuberculosis returned as the global leading cause of death by infectious disease, overtaking COVID-19, reportedly responsible for the death of 1.25 million (WHO, 2023). As of 2023, The World Health Organization (WHO) recommends the use of bedaquiline for the treatment of multidrug- and rifampicin-resistant tuberculosis; however, only about 40% of people with drug-resistant tuberculosis recieved treatment in 2023 (WHO, 2023). Bedaquiline, approved by the US Food and Drug Administration (FDA) for the treatment of tuberculosis in 2012, was the first new approved tuberculosis treatment in over 40 years (Mahajan, 2013). It was produced solely by Johnson and Johnson (J&J) under the name "SIRTURO©" from the time of its approval until J&J's primary patent expired in 2023. J&J's primary patent allowed for a monopoly on production and distribution of the life-saving drug in all patented countries, leading to the company demanding high prices ($272 for 6 months of treatment), significantly reducing the availability of the drug to low- and middle-income countries (MSF, 2023). Upon the primary patent expiry in 2023, J&J reduced the price to $130 for the entire 6-month treatment, and a generic producer, Lupin, offered the same treatment for $194 (Stop Tb Partnership, 2023). J&J used the patent system to increase the profit margin on bedaquiline to recuperate losses associated with the drug's research & development (R&D), while millions were going untreated and passing away in low-income areas due to the higher cost of the treatment (Cohen et al., 2000). The aim of this project is to determine whether patents within the pharmaceutical industry drive innovation as intended, or if they are a system abused by pharmaceutical companies to demand high prices for lifesaving drugs and to propose a potential solution to the patent-driven accessibility issues associated with new, life-saving drugs.

An economic analysis study found that inventions within the pharmaceutical industry are more dependent on patent protection than any other industry, finding that 65% of inventions in the pharmaceutical industry would not have been introduced to the market without patent protection, with the chemical industry being 2nd most dependent at 30% (Mansfield, 1986). The pharmaceutical industry's dependence on patents is because the cost of drug innovation is high, while the cost of mimicking, also known as generic drug production, is comparatively low (Gabrowski, 2002). Therefore, pharmaceutical companies rely on patents to guarantee a temporary monopoly on the market, allowing for time to overcome the costs associated with drug development and gain a significant profit before generics are produced.

While the patent system incentivizes pharmaceutical companies to invest money into diseases affecting low-income areas, like tuberculosis and malaria, pharmaceutical companies have developed ways to manipulate the system to ensure longer monopolies, such as evergreening and secondary patents. Evergreening is the practice of continuing to apply for and obtaining patents of "doubtful validity or applicability" (Hemphill, 2012) for name-brand drugs to stop other companies from manufacturing generics. Secondary patenting is the practice of applying for parallel patents, such as for different formulations, new uses, alternative forms of the active pharmaceutical ingredient, etc. (Sampat, 2017). Both practices decrease the accessibility of life-saving drugs to developing countries because the high price established under the primary patent is maintained for a longer period. J&J attempted to enforce secondary patents on the bedaquiline production process following the primary patent's expiration in 2023; however, they were met with much scrutiny and eventually agreed to not enforce the patent in low- and middle-income countries (J&J, 2023).

Patent policies, like the World Trade Organization's (WTO) 1995 agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the Drug Price Competition and Patent Term Restoration Act of 1984, were implemented as an attempt to globally standardize the patent system and balance the access to and innovation of new drugs (Sampat, 2017 & Hemphill, 2012). However, due to the presence of practices like evergreening and secondary patents, there clearly exists many faults in the patent system, specifically within the pharmaceutical industry, that limit the accessibility of new technology to low-income areas.

This project will analyze how pharmaceutical patents affect the innovation of and accessibility of life-saving medications to developing countries using J&J's bedaquiline patenting strategy as a case study. Evidence will be collected through systems analysis using Actor-Network Theory (ANT), as well as by investigating current patents on pharmaceutical products. The results from this analysis will be used to propose a solution to the determined problems in the patent system, specifically focusing on balancing technological innovation and the accessibility of novel therapies to those in need.

Conclusion

The deliverable for the technical problem discussed in this paper will be the design of a tuberculosis mRNA vaccine manufacturing process to address the lack of global accessibility of effective tuberculosis treatments. The STS research paper will analyze how pharmaceutical patents affect the innovation of and accessibility to novel, life-saving medications for developing countries using J&J's bedaquiline patenting strategy as a case study and will offer a solution to effectively balance innovation and accessibility within the pharmaceutical industry. Actor-network theory will be used to determine how human and non-human actors influence the distribution of medications globally, the development of patent policy over time, and the usage of patent policy by pharmaceutical companies. The compiled results of these deliverables will work together to propose solutions to the worldwide tuberculosis epidemic by proposing a novel, effective therapy production process and a system in which the therapy could exist that would ensure maintained accessibility of the therapy to those with tuberculosis around the world without demanding unreasonable stakeholder losses.

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