An Actor-Network Theory Analysis of the Threat of Evergreening to the U.S. Trastuzumab Biosimilar Market

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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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Introduction

Through the Biologics Price Competition and Innovation Act of 2009, Congress opened the U.S. market to biosimilars (Fidelity Investments, 2020). According to the FDA, a biosimilar is a biological product that is "highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product." Biosimilars follow abbreviated approval pathways compared to the reference, or original, drug product. This accelerated timeline and reduction in requirements provides biopharmaceutical companies with an opportunity to create their own version of a successful biologic. The purpose of allowing biosimilars in the U.S. was to provide additional treatment options, increase access to medications, and lower health care costs by allowing direct competition (Fidelity Investments, 2020). Although Herceptin biosimilars, which treat breast-cancer, were able to successfully claim part of the European market, the newer U.S. biosimilar market may not find the same success. While it is true that four out of the five Herceptin biosimilars successfully settled patent litigation with Genentech to reach the U.S. market, the patent trouble may not be over (Fish & Richardson, 2020). The U.S. biosimilar markets are threatened by evergreening. Evergreening is a strategy employed by pharmaceutical companies to extend market exclusivity after their patent's expiration. A company will make a slight change to its drug or its drug's application and receive a new 20-year patent to effectively block competition. If successful in the U.S., Genentech can remove biosimilars or render them uncompetitive by the slight superiority of their brand name drug (Eddy, 2020).

Throughout this paper, I will use Actor-Network Theory (ANT) to show that evergreening is a threat to the U.S. biosimilar network, specifically for Herceptin. By recognizing evergreening as a rogue actor in the network, we will see the fragility of biosimilar

pricing in the U.S. and form a better understanding of how U.S. patients rely on more than biopharmaceutical companies to provide them with cancer treatment. I argue that the benefit of biosimilars to patients within the network is threatened by evergreening due to Genentech's actions and the FDA's policies and current inaction. In my analysis, I will define the complex U.S. Herceptin biosimilar market actor-network, show Genentech's ability to disturb the network by using evergreening, and explain how the FDA is not fulfilling its role in the network, which is helping Genentech succeed in evergreening. To support my analysis, I will use patents records that show Genentech's intention to use evergreening, litigation records between Genentech and companies proposing biosimilars in both the U.S. and Europe, and current FDA rules and regulations.

Background

Biologics are drugs produced from living organisms. They are more complex than small molecule drugs, so they are more difficult and expensive to produce. Herceptin is a mAb that targets HER2+ breast cancer. It was created by Genentech, and its generic name is trastuzumab. Since 2009, there have been 28 total biosimilar FDA approvals and 18 launches to the U.S. biopharmaceutical market (FDA, n.d.b). Five of these approvals went to biosimilars for Herceptin, the last of which launched April 2020 after being approved January 2019. For biologics, patents only last for 20 years (Feldman, 2018). After 20 years, biosimilars are allowed to enter the market and compete for patients, which effectively ends a monopoly and begins competitive pricing. Because biologics are so complex, they are difficult to completely replicate on a small scale and manufacture on a large scale. Biosimilars require hundreds of millions of dollars in investments, and many are unsuccessful in reaching the market due to strict FDA requirements.

Literature Review

Several scholars have analyzed evergreening in the pharmaceutical world, especially amongst the larger blockbuster drugs, including Herceptin. Scholars have shown that evergreening through over-patenting is a common tactic employed by biopharmaceutical companies in the United States, and they have shown that there are flaws within the patent system that allow for these companies to legally extend their monopolies. However, scholars have not yet adequately considered how fragile the United States biosimilar market currently is or the complex relationships between and the differing goals of each involved party. I will review two scholarly articles that represent common arguments surrounding biosimilars.

In the paper "May your drug price be evergreen," Feldman compiled 10 years of data published by the FDA in its Orange Book, which holds all of the information on small molecule drugs (FDA, n.d.a). He analyzed the data to discover trends between new patents and whether the drug being filed for was new or already on the market (Feldman, 2018). Feldman found that "78% of the drugs associated with new patents in the FDA's records were not new drugs coming on the market, but existing drugs." This means that a large majority of patents were for existing drugs that were already protected by their original term of market exclusivity. Many pharmaceutical companies also produce biologics in addition to small-molecules, including Genentech. Feldman found of the drugs that had patents or exclusivities added, "80% of those had an addition to the Orange Book on more than one occasion, and almost half of these drugs had additions to the Orange Book on four or more occasions". This shows that companies who are willing to evergreen are willing to do so multiple times, so despite Feldman looking at small-molecule data, trends are likely similar for biologics. Feldman argued that to protect competition

within the medical sphere, there should be "one-and-done in which a drug would receive one period of exclusivity, and only one."

In the paper "Improving oncology biosimilar launches in the EU, the USA, and Japan: an updated Policy Review from the Southern Network on Adverse Reactions," Bennett et. al explored the launches of therapeutic oncology biosimilars, including those for Herceptin. (Bennet et al., 2020). The analysis showed that "market launches of oncology drug biosimilars in the USA have been more adversely affected by patent litigation considerations than launches in either the EU or Japan." This study outlined the multiple legal types of entry to U.S. biosimilar markets including pay-for-delay agreements and launching at risk. In a pay-for-delay agreement, the original biologic company pays the biosimilar company to delay launching for a specified period of time. Four of the Herceptin biosimilars used this approach. When launching at risk, the biosimilar company launches before patent litigation is settled and risks a large financial penalty if it loses litigation. Amgen successfully used the launch at risk approach for its Herceptin biosimilar. This paper recommends supporting competition by reducing the side-stepping of FDA requirements. This is done by requiring the original biologic company to sell its product to companies developing biosimilars and simplifying agreements allowed between reference product and biosimilar companies.

Both Feldman and Bennet et. al.'s studies found inefficiencies in U.S. biosimilar markets and proposed methods to support competitive markets. However, neither fully consider the complexities of the roles of companies and the FDA in the biosimilar markets. Feldman does show that pharmaceutical companies use evergreening, but he fails to acknowledge that many new patents may be for clinical improvements of existing drugs, which can be patented. It is not evergreening and would not unfairly disturb a biosimilar network, but his suggested "one-and-

done" strategy makes these fair patents impossible. Bennett et al. provided suggestions to reduce patent litigation and decrease biosimilar time to market, but they failed to fully consider why companies make agreements within the biosimilar market, or why the FDA requires a longer approval time. In my analysis, I will define the roles of different companies and the FDA in the U.S. Herceptin biosimilar network to show the fragility of the U.S. Herceptin biosimilar network due to Genentech becoming a rogue actor and employing evergreening.

Conceptual Framework

The impact evergreening has on the U.S. biosimilar network can be analyzed using Actor-Network Theory (ANT). ANT examines complex relationships between both human and nonhuman actors that come together to create a dynamic network (Callon, 1987). ANT relies on network builders to create a socio-technical network in which actors have evolving power dynamics. ANT considers science and technology in the making to analyze the complexities and nonlinearities of the development of science and technology.

Within ANT is Callon's concept of translation. Translation describes the process of forming and maintaining an actor-network (Callon, 1986). The stages of translation are problematisation, interessement, enrolment, and mobilisation. In problematisation, the primary actors, or the network builders, define the problem and identify the essential actors to solve that problem. The essential actors must be shaped to serve the network's goal; this is the initial groundwork to establish the network. In interessement, the primary actors seek out additional actors to participate in the network and contribute to the solution in a way that benefits the primary actors' goals. In enrolment, the recruited actors begin to contribute to the network in interrelated roles. Enrolment requires actors to carry out their assignment as intended by the

primary actors. In mobilisation, the primary actors attempt to maintain control of the network and serve as spokesmen to maintain the network's initial purpose.

It is important to note that Callon acknowledges how a network can fail at any step of the way – especially when an actor does not act in good faith for the network's original purpose (Callon, 1986). In the following analysis, this will be referred to as a rogue actor. A rogue actor can make a network unstable by disturbing existing connections and actors and by acting outside of its specified network role. Callon asserts that "for the entities [a network] is composed of, whether natural or social, could at any moment redefine their identity and mutual relationships in some new way and bring new elements into the network." This is important when analyzing the U.S. biosimilar network because it is always vulnerable to change through its actors' actions. Callon's translation will allow me to show where the U.S. biosimilar market actor-network became vulnerable, and how evergreening is the actor threatening the network's stability as a rogue actor.

Analysis

Network Formation

Reconstruction of the U.S. biosimilar market actor-network will provide the background necessary to analyze its current fragility by showing the importance of each role and relationship to the success of the network. The U.S. biosimilar market involves multiple human and nonhuman actors who are interconnected in various ways. I will begin by outlining essential human and social group actors, and then I will outline essential nonhuman actors. For the U.S. trastuzumab biosimilar market, the network builders include the scientists and engineers that create the actual biosimilars. Without the scientists and engineers working to create the drugs, there would be no network, because there would be no need for a biosimilar market. For the

network builders, the goal would be to design a drug that could effectively compete with Herceptin. Potential motivation for these network builders would be money for the company they work for, recognition for developing a successful biosimilar, and providing a more accessible option for patients (Moorkens et al., 2016).

Additional human actors include Genentech and the biosimilar companies. Their decisions to compete and produce their drugs help to advance the network. The teams of lawyers and business strategists at both Genentech and the biosimilar companies are actors. Genentech's role in the biosimilar actor-network would be to maintain market share and improve the place of Herceptin. Later in this analysis, I will show that this is not happening, and it is threatening the network. On the biosimilar company side, the purpose of the lawyers and business strategists would be to understand patents and support their biosimilar within the market. The FDA is another important actor because they determine the landscape of biosimilars, and they set the approval timelines (Fidelity Investments, 2020). Additional human actors that are important to note but are not essential to this analysis are patients and physicians. Patients should be kept at the center of the network because the drugs are for them – they want the biosimilar market to succeed because it effectively lowers the cost of their life-saving medicine. Physicians are important because they prescribe the drug, and their trust or distrust of a biosimilar will determine if it stands a chance against the other options, especially the established Herceptin (Cuellar, 2020).

There are many important nonhuman actors in this actor-network. Herceptin itself is a nonhuman actor. Its efficacy as a drug and success as a breast cancer treatment has generated a multibillion-dollar market, and this is why companies want to have a stake in the market. The biosimilar drugs are nonhuman actors. Without them there is no competition for Herceptin. The

Biologics Price Competition and Innovation Act of 2009 is a nonhuman actor. It made it legally possible for biologics to be sold in the US (Fidelity Investments, 2020). The FDA's Purple Book is an additional nonhuman actor. In this network, its purpose is to hold all known information about biosimilars.

I will now illustrate important connections within the actor-network. The FDA has to determine the approval pathway for biosimilars, and they have to actually approve the biosimilars. They require a high standard of safety for biosimilars, and this hopefully strengthens physician and patient trust. The teams of lawyers at Genentech and at each biosimilar company work against one another to support their own company's drug. At Genentech, they write patents and defend patents to maintain Herceptin's prominence. At the biosimilar companies, they work against Genentech to dismiss each patent and prove their innocence at infringement. The biosimilar companies much decide a launch strategy for the biosimilar. For example, Amgen deployed the At-Risk Launch strategy, which means they launched before litigation was over (Bennet et al., 2020). This risked millions of dollars in penalties, but with success it allowed them to more quickly join the market and capture market share. Another important relationship is between the Purple Book, the FDA, and physicians and patients. The Purple Book is updated and maintained by the FDA, and it provides physicians and patients with information regarding biosimilars (FDA, n.d.b). Later in my analysis, I will explain how the limited information found in the Purple Book due to the FDA's decisions has made it more difficult for biosimilars to enter the market. I will also illustrate their current plan to fix this issue to support the biosimilar market.

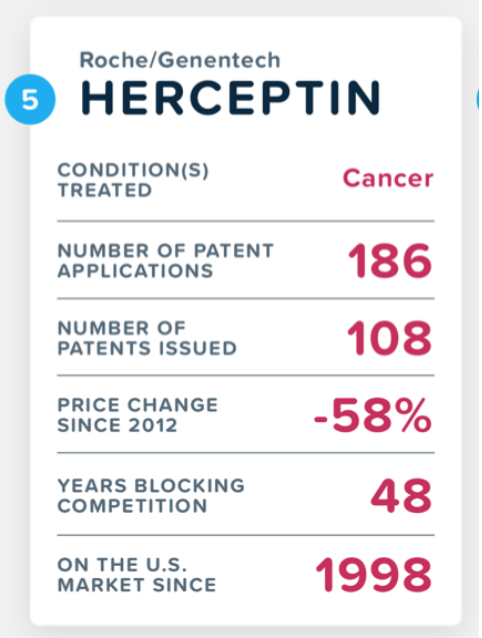
Genentech's Role

I will now explain Genentech's role in the U.S. trastuzumab biosimilar market and show how their use of evergreening is threatening the actor-network. Genentech is the company that produces Herceptin, which is the reference product for all five trastuzumab biosimilars. Genentech's role in the U.S. biosimilar market is as a company competing against biosimilar companies to maintain market share. Because Genentech owns the reference product, they have the competitive advantages that come with being the original, such as established relationships with hospitals and physicians, patient trust due to years of success, and brand-name familiarity (Moorkens et al., 2016). For the biosimilar market actor-network to function as intended, Genentech needs to accept this role as a leader in a now competitive trastuzumab market, as is important in the enrolment stage of translation.

Unfortunately, Genentech has not accepted its role in the U.S. biosimilar market. In fact, they are attempting to stifle the trastuzumab biosimilar market altogether. As shown in Figure 1, Genentech and its parent company Roche have attempted to push 186 patents through to extend their market exclusivity (I-Mak, n.d.). 108 of those patents have been successfully issued, and they could potentially bring 48 years of market exclusivity (I-Mak, n.d.).That is more than double the 20 years of intend market exclusivity for drugs. Using these patents, Genentech and Roche can delay or prevent biosimilar companies from entering the market, and they can potentially close the market by fighting

Figure 1

Herceptin Patent Information



biosimilar companies through patent litigation. Genentech and Roche have relentlessly pursued litigation to eliminate biosimilars for Herceptin. Of the five biosimilars that have reached the market, four reached settlements to delay launch. The fifth is still undergoing litigation.

In the biosimilar actor-network, Genentech and Roche's role is to support Herceptin and compete with the biosimilar companies. However, they clearly are abusing the patent system to extend market exclusivity and block biosimilars. In response to questions about extending market exclusivity, Roche said "patent and intellectual property laws enable scientific innovations and our ongoing ability to discover and develop breakthrough medicines for patients depends on the protection of our patent and IP rights" (Liu, 2018). While this is true and correctly describes the purpose of patents, it is not an adequate defense for evergreening. Herceptin had its 20 years of market exclusivity, and it did provide an ability to discover and develop breakthrough medicines for patients. Between 1998 and 2017, there were $88.2 billion in sales of Herceptin. The upper threshold R&D cost of trastuzumab is $2.827 billion, which means Genentech made approximately $31.20 for every risk-adjusted dollar that went into their R&D (Tay-Teo, 2019). This means that from the 20 years of patent exclusivity, Genentech made enough money to develop over 30 drugs of the same magnitude as Herceptin. Of course, this is unlikely due to the complex nature of these drugs, but the argument that 20 years is not enough to invest in future drugs does not follow the economic analysis. It shows that Genentech and Roche are willing to extend Herceptin's market exclusivity using additional patents and intellectual property laws, and that they will outwardly justify it.

This willingness to employ evergreening is a willingness to block biosimilars and effectively destroy the U.S. biosimilar trastuzumab actor-network. Without any biosimilars, there is no biosimilar network. They continue to attempt to destabilize the network, despite biosimilars

having been legally released. The list price per 150 mg vial of Herceptin is $1,558, which results in a price of $4,675 per month (Chase, 2020). Each biosimilar option is priced for approximately 10-30% savings. Herceptin biosimilars clearly result in substantial savings for patients, and they have high potential to increase accessibility for patients. If Genentech and Roche are successful at evergreening, those savings will disappear for patients because there will be no competition driving prices down. Biosimilars and biosimilar companies will no longer be able to function, and the actor-network will be destroyed.

The FDA's Role

I will now explain the FDA's role in the U.S. trastuzumab biosimilar market to show how their current policies and inaction is threatening the actor-network. As the regulatory agency for biologics, the FDA has a powerful role in the U.S. biosimilar actor-network. It dictates approval timelines and protocols. It also keeps a public record of all licensed biologics in the Purple Book. The Purple Book includes the exclusivity and the biosimilarity for each drug. It serves as a basis for both patients and physicians when looking at treatment options. The Orange Book is the equivalent for all approved drug products with therapeutic equivalence evaluations, and it is the FDA's gold standard (FDA, n.d.a). I will highlight key differences between the Purple Book and the Orange Book that show potential causes of fragility for the biosimilar actor-network. This fragility makes the actor-network more vulnerable to rogue actors, such as Genentech evergreening. As of March 15th, 2021, the Purple Book has not been updated since August 3rd, 2020 (FDA, n.d.b). On the other hand, the Orange Book is current through March 2021 (FDA, n.d.a). If patients and physicians are referencing the Purple Book in the same way as the Orange Book, they will not have the most up-to-date information. When it comes to life-or-death treatments, up-to-date information is essential. If a biosimilar has been approved since last

August, there will be no evidence it exists in the Purple Book, which is supposed to hold all FDA known information. Additionally, the Purple Book is not nearly as comprehensive as the Orange Book (FDA, n.d.b). Unless the FDA treats the Purple Book with the same amount of consideration as the Orange Book, biosimilars have additional obstacles to overcome. Fortunately, the Purple Book Continuing Act was signed into law on December 27, 2020 (Shelton, 2021). This requires that the FDA updates the Purple Book at least every 30 days. This has clearly not yet happened, but it is a positive sign for biosimilars. It also requires that certain patents be listed in the Purple Book alongside their expiration dates. Once this occurs, it will be clearer when a company is attempting evergreening, and it will be easier to fight. This will help protect and strengthen the U.S. biosimilar market. The FDA's inaction in updating the Purple Book is an example of them not fulfilling their enrolment in ANT to the fullest extent.

In Europe, the patent protection for Herceptin expired in 2012. Three biosimilars were able to capture 38% of the trastuzumab market within 10 months of their introduction (Cuellar, 2020). The Herceptin biosimilars were able to overcome the typical barriers to acceptance, such as complex and expensive manufacturing processes, difficulty to differentiate from the brand drug, and establishing relations with hospitals and physicians (Moorkens et al., 2016). The European equivalent of the FDA is the European Medicines Agency (EMA). The EMA has slightly different rules for biosimilars than the FDA, and they likely contribute to the success of biosimilars in Europe. A recent study of U.S. biosimilar approvals found that trials to obtain FDA approval were larger, longer, and more costly than the trials for the reference drug (Moore et al., 2021). This is not the case for EMA biosimilar approvals. In addition, the FDA requires animal studies for a biologic product, and the EMA does not. The EMA has the same safety and quality standards for biosimilars as it does for reference products, but it uses the reference

product to guide biosimilar studies and save money and time. The FDA intends to do so, but it does not. This has prevented biosimilars from reaching the market in a timely manner, and in turn it affects the patients in the actor-network by limiting the competitive pricing biosimilars bring. Figure 2 shows that even since the U.S. allowed biosimilars, the European biosimilar market has grown more rapidly (Harston, 2021). The decline in 2021 is likely due to the Covid-19 pandemic shifting resources.

Figure 2

U.S. and European Biosimilar Product Comparison

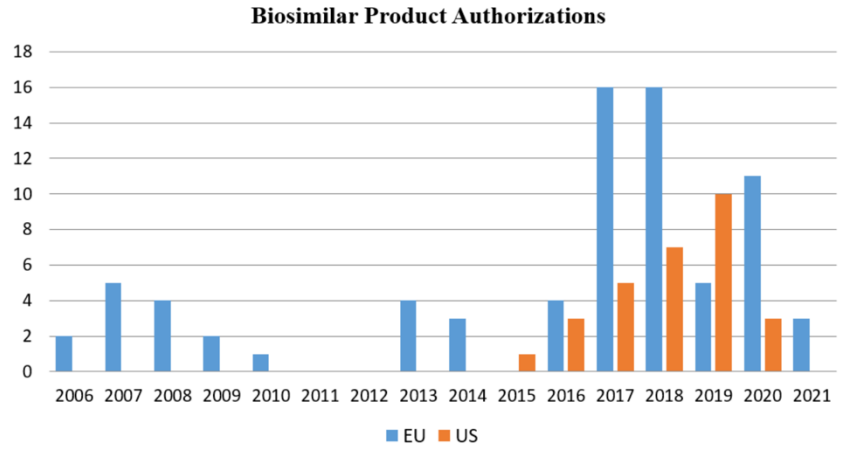


Figure 2 makes it clear that in years biosimilars are successful in the European market, they are not nearly as successful in the U.S. markets. Europe does not have more lenient safety standards, but it does allow for an accelerated approval pathway when compared to the US. This time is critical for patients because it creates change in prices and increases the potential for access to these medicines. The FDA functions for patients, including those affected by the biosimilar network. Its role is to approve medicines that are safe and effective, but because of the complexities of the biosimilar actor-network, it is important to note that FDA approvals also impact drug cost. Drugs must be safe and effective, but if they are not affordable, patients will not be able to use them.

Conclusion

Throughout this paper, I have used the sociotechnical framework of ANT to outline important relationships and power dynamics within the U.S. trastuzumab biosimilar market. I have shown the fragility of the actor-network due to the evergreening strategy, and I have shown how this will directly impact patients' ability to access life-saving medicines. By specifically looking at the role Genentech plays within the actor-network, it is clear that Genentech intends on limiting entry into the biosimilar market by leveraging patents and intellectual property licenses, despite the end of its 20 years of market exclusivity. By looking at the FDA's current policies regarding biosimilars and comparing them to the EMA, it is clear that the FDA is not fully performing its duty to provide patients with access to the treatments they need.

The scientists and engineers designing biosimilars are not the ones who are disrupting the biosimilar market, but the companies they work for and the guidelines they design under are. By continuing to create biosimilars and investing effort into making them as safe and effective as possible, scientists and engineers can improve the chances of success within a biosimilar market, and they can strengthen the competitive nature of the markets. In design, it is important to remember that a drug will be a point of profit for the company, but it will also be a lifeline to patients in desperate need. Scientists and engineers rely on additional actors to reach patients, but it all begins in with them in the lab.

Word Count: 4038

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