1-2022

An Evaluation of the Biologics Price Competition and Innovation Act and its Impact on Innovation in the Pharmaceutical Industry

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by

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A Thesis Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science in Science, Technology, and Public Policy

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January 2022

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ABSTRACT

In the pharmaceutical industry, innovation is vital to bring more life-saving treatment options to patients. However, pharmaceutical manufacturers face strict safety and effectiveness guidelines set forth by the U.S. Food and Drug Administration (FDA), before being able to place their innovations on the market. In attempts to balance the need for continuous innovation and stringent regulation, policymakers created the Biologics Price Competition and Innovation Act (BPCIA) of 2009. The BPCIA allows biosimilars manufacturers to enter a shortened FDA approval pathway and provides incentives for biologics manufacturers with the aims to decrease cost and increase access to medications for patients by stimulating innovation within the industry.

In this thesis, I empirically investigate the impact of the BPCIA on biopharmaceutical innovation. I utilize public data from the FDA and United States Patent and Trademark Office (USPTO) to measure these innovations and conduct regression analyses to estimate the effects of the BPCIA on related drug and patent approvals. My analysis shows that since its enactment, the BPCIA has increased innovation in biopharmaceuticals. Based on my results, I discuss implications for policymakers and future researchers.

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1 INTRODUCTION

The continuous creation of new ideas and products to maintain market standing is known as innovation—more so defined as the creation of novel inventions that are then used to further the knowledge of the industry and produce new products for consumers (Soon, 2013; U.S. Department of Health and Human Services, 2020). Manufacturers need to innovate to maintain market standing, which is especially important in the pharmaceutical industry because pharmaceutical manufacturers face strict guidelines before they can market their innovations.

The government highly regulates pharmaceutical development and manufacturing to protect the health and safety of consumers. This government control is necessary; there is a fine line between beneficial and harmful effects when it comes to medicine, so development and manufacturing must be closely monitored. However, this can discourage companies from working on breakthrough innovations. The United States Food and Drug Administration (FDA) is the agency that oversees pharmaceuticals, creates strict regulations and a time-consuming review process to confirm that a new drug is both safe and effective. To meet these standards, pharmaceutical manufacturers must spend large amounts of both time and money to get their product approved, which slows down how fast they can place their innovations on the market.

Policymakers are aware of the laborious process needed to approve pharmaceutical innovations and have made steps to lessen the burden for manufacturers, such as creating streamlined drug approval pathways. One of the newest attempts is the Biologics Price Competition and Innovation Act (BPCIA) of 2009, which has the goal "to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition" (U.S. Food and Drug Administration, 2019). To achieve this goal, the BPCIA creates an expedited FDA approval pathway for the creation of biosimilars and provides

other incentives to biologics manufacturers to promote the creation of new drugs, which I will explain in detail in Section 2.1.

As with any new policy, it is important to evaluate its outcomes to assess the level of success to provide recommendations. Despite the importance of evaluating the BPCIA, only one researcher has empirically examined its outcomes suggesting that the BPCIA increases innovation, but could use some improvements (Addivinola, 2018). As I will discuss in the literature review (Section 3), other research indicates that the BPCIA creates a more complex set of outcomes than originally expected, with its outcomes of patient accessibility and price reduction relying on innovation occurring. Additionally, researchers express doubts that the incentive of market exclusivity provided by the BPCIA is aiding in meeting its goals (Blackstone & Fuhr, 2012; Shepherd, 2015).

Due to the lack of research assessing the BPCIA and the doubts cast by scholars, it is critically important to evaluate this policy to determine if it has successful outcomes or if policy changes are recommended. Specifically, the effect the BPCIA has on pharmaceutical innovation needs to be studied because it is required for other goals to be met. Therefore, the goal of this thesis is to take an in-depth look at the BPCIA and empirically assess its impact on pharmaceutical innovation since its enactment in 2010 using statistical analysis.

To do this, I utilized the FDA "Purple Book: Lists of Biological Products" and the USPTO PatentsView databases to compile my data. To collect patent data, I created a list of relevant Cooperative Patent Classification (CPC) codes to pull only relevant patents from the database. Such a list has not been made before; the search method I created as well as list of CPC codes will be useful for future researchers studying patents. With this data, I both graphically and

statistically analyzed the estimated effects of the policy on innovation. After presenting my findings, I discuss the implications my research presents for policymakers and future researchers.

2 BACKGROUND

2.1 BASIS OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT

2.1.1 BPCIA LEGISLATION

Biologics became more commonplace in the late 1990s, which prompted the amendment of the Public Health Service Act (PHSA) in 1999, allowing for biologics to be approved under a Biologics License Application (BLA) (Biological Products Regulated Under Section 351 of the Public Health Service Act, 1999). Before this guidance, the FDA approved biologics via a New Drug Application (NDA), despite biologics being inherently different and more complex than the chemical drugs typically approved under an NDA (Thakore, 2016).

The BPCIA, which is part of the Patient Protection and Affordable Care Act, amended the Public Health Service Act (PHSA) to include section 351(k) in 2009 under the Obama Administration. The BPICA authorized the U.S. Food and Drug Administration (FDA) to create a streamlined approval pathway for biosimilars via an FDA Biologics License Application (BLA) in place of the typical 351(a) pathway (Lietzen et al., 2010 & Rifkin, 2018).

The FDA states that the goals of the BPICA are "to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition" (U.S. Food and Drug Administration, 2019). To reach these goals, the FDA relies on manufacturers to continue to innovate. The Act itself creates an incentive for biosimilar manufacturers: there is a streamlined approval process. The BPCIA also provides exclusivity periods for biologics: a 4-year exclusivity period from the time a reference product is first licensed where a biosimilar application may not be submitted and a 12-year exclusivity period where a biosimilar application cannot be approved (U.S. Department of Health and Human

Services [USDHHS] et al., 2015a). These exclusivity periods give the original manufacturer time to make profit on their product without facing competition from others, which incentivizes companies to continue innovating new products (Shepherd, 2015).

The BPCIA does not protect biosimilar manufacturers from patent infringement, a key concern for biosimilar manufacturers. Instead, the BPCIA lays out a framework for patent litigation, with the aim to settle any patent disputes between the biosimilar applicant and reference company prior to FDA approval of the biosimilar (Calvo & Shea, 2020). A biosimilar applicant must notify the reference company when they first submit an application, and then the reference company must identify any patents that could be infringed upon. Since the biosimilar company relies on data from the original biologic to create their drug, it is highly likely that they will end up using intellectual property owned by the reference company (Ainsworth & Wyatt, 2019). The companies then communicate back and forth to settle any disputes that arise, which policymakers call the "patent dance" (Ainsworth &Wyatt, 2019; Calvo & Shea, 2020).

However, the patent litigation process set forth by the BPCIA is quite vague, meaning a biosimilar company is not legally obligated to disclose their application or a reference company their related patents (Margolis; 2013). While patent litigation is necessary, it can actually discourage companies from creating both biosimilar and original biologic drugs. Instead of innovating new drugs, reference companies focus on blocking biosimilar companies during the "patent dance," and biosimilar manufacturers are discouraged due to fear of patent infringement (Balckstone & Fuhr, 2012; Shepherd, 2015).

2.1.2 PRIOR LEGISLATURE

The BPICA is not an entirely new legislation. It is modeled after the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, as well as the European Medicines Agency's successful 2004 biosimilar approval pathway, which I discuss in more detail next (Tvetenstrand, 2015). As technological advances increased in the years after the Hatch-Waxman Act, many pharmaceutical companies began manufacturing biologic drugs, which are difficult to fit within the provisions of the existing act. Similar issues to those that preceded the Hatch-Waxman, such as patent disputes and a long, costly approval process, as well as seeing the success of the European Union's (EU) biosimilar pathway, prompted Congress to enact the BPCIA. While these laws are not the focus of this research, their passage and ultimate success are some of the main reasons the BPCIA came to fruition.

2.1.2.1 The Hatch-Waxman Act

In the early 1980s, the United States Congress became re-focused on medical innovation and the cost of healthcare due to industry shortcomings highlighted by patent disputes at the time and the work of Representative Henry Waxman and Senator Orrin Hatch. Numerous patent disputes were occurring because it was not legal for a generic company to utilize a reference company's data until after the patent expired (Schacht & Thomas, 2012). Additionally, drug manufacturers were unhappy because they would lose time on their patent period while waiting for FDA approval (Thomas, 2016).

Under Waxman and Hatch's guidance, Congress addressed these concerns by passing the Hatch-Waxman Act to increase market competition between drug manufacturers and lower the cost of medicines for patients (Billings, n.d.). This established an abbreviated FDA approval pathway for generic drugs, the Abbreviated New Drug Application (ANDA), which allows

generic manufacturers to use data compiled by the original manufacturer when establishing safety and efficacy (Schacht & Thomas, 2012). Generic companies could also utilize this data while the original company's patent was still in effect: Hatch-Waxman protects the generic company from patent infringement, provided it does not file an approval to market their generic until the original patent term has expired (Thomas, 2016). While the BPCIA does not include these protections, it does set forth a framework for related patent litigation.

The infringement protections encouraged generic companies to produce drugs, but original manufacturers still needed the incentive to innovate new medicines. Therefore, the Hatch-Waxman Act also provides patent term restoration. Typically, a patent term is set from the date it is first filed and continues to run even while a company conducts clinical trials and waits for FDA approval. Hatch-Waxman allowed for the patent term to be extended to make up for time lost waiting for approval (Schact & Thomas, 2012). This provides original manufacturers the incentive to continue innovating because they will have more time to collect revenue on their products without competition (Billings, n.d.). Again, the BPCIA modifies Hatch-Waxman by instead providing a 12-year exclusivity period for original biologics.

There is some evidence of the Hatch-Waxman Act's success. The Congressional Budget Office (CBO) has attributed the of rise from 18.6% in 1984 to 63% in 2007 of prescriptions filled for generic drugs to the Hatch-Waxman Act (Schacht & Thomas, 2012). Additionally, the CBO reported that drug company increased their research and development (R&D) spending steadily after congress passed Hatch-Waxman, reaching $50 billion in 2008 (Thomas, 2016). This indicates that companies were innovating more and therefore increasing market competition as per the law's goal. These successes have saved consumers an estimated $300 billion annually, reaching the second goal of lower cost for consumers (Billings, n.d.).

2.1.2.2 European Medicines Agency Biosimilar Regulation

In 2004, the European Union (EU) introduced the first formal regulatory pathway for biosimilar drugs. In the EU, the European Medicines Agency (EMA) oversees pharmaceutical regulation. This organization brought its biosimilar pathway to fruition with the intention of "balance[ing] patient safety and sound science with the goal of delivering biologic therapies at lower cost" (European Union Experience, 2019). This biosimilars medicine pathway relies on showing that the biosimilar is "highly similar" to a reference medicine "in terms of structure, biological activity and efficacy, safety, and immunogenicity profile" (European Medicines Agency [EMA] & European Commission, 2019). Because researchers are using a reference medicine as the basis for development, the EU pathway allows for a shift in data requirements for approval of a biosimilar medicine.

Research for a biosimilar medicine requires comparative quality studies, resulting in less time in the clinical studies phase, which creates a faster path to the market (EMA & European Commission, 2019). This framework showed success when the EU approved the first biosimilar in 2006. Since then, the EU biosimilars pathway has been used as a framework for biosimilar development across the globe; lawmakers utilized knowledge of this pathway when drafting the BPCIA (European Union Experience, 2019).

2.2 THE DEVELOPMENT OF BIOLOGICS AND BIOSIMILARS

All pharmaceuticals move through a development and approval process that follows the same basic timeline. However, chemical and biologic drugs are vastly different from each other. Chemical drugs have simple, easy to manufacture structures; this means that they can move through FDA approval quickly and are relatively inexpensive to manufacture and purchase (Thakore, 2016). Biologics are large, complex molecules that are produced in a living system.

This complicated nature makes them difficult to manufacture and requires a lengthy FDA approval process (U.S. Food and Drug Administration, 2017). A comparison of the size and complexity of chemical and biological drugs can be seen in Figure 1.

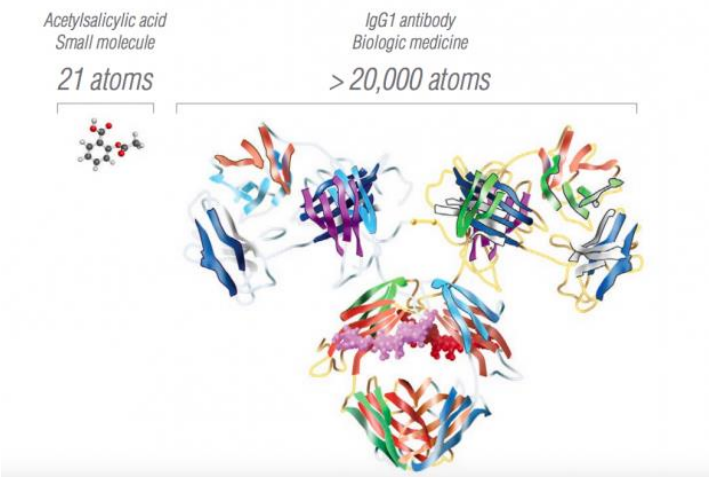

Figure 1. Aspirin on the left compared to an Immunoglobulin G Antibody on the right (Tvetenstrand, 2015).

Despite the inherent differences between small and large molecule drugs, such as the size and complexity, as seen in Figure 1, the general development process for all pharmaceuticals is the same: Discovery, Preclinical Research, Clinical Research, Review, and Post-Market Safety Monitoring. However, policies such as the Hatch-Waxman Act and BPCIA redistribute or shorten the time spent in each phase of development, which is best visualized as an inverted pyramid, as shown in Figure 2.

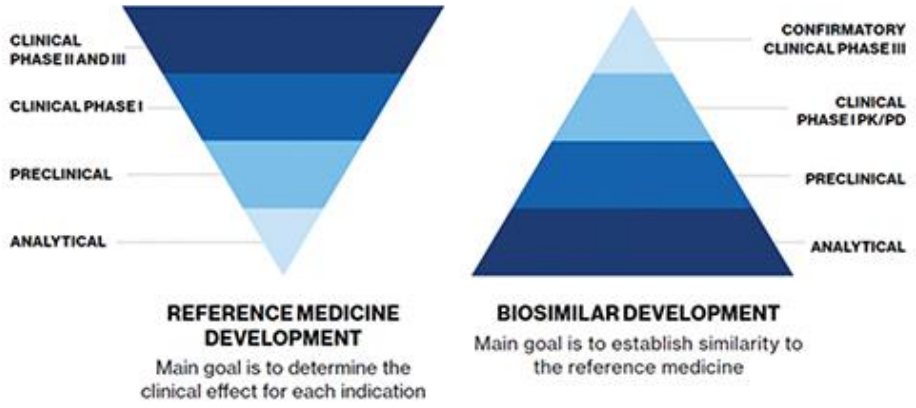

Figure 2. Redistribution of importance and time spent in biosimilar drug development as compared to reference drug development (Cohen, 2019).

As seen in Figure 2, the phases of development that are the most demanding for each type of drug are the largest parts of the pyramid. While the figure excludes the last steps, both types of drugs move on to FDA approval and post-market monitoring after completing phase III trials. Despite the redistributed pathway, biosimilars must still go through a meticulous approval process to prove that they are just as safe and effective as their biologic reference product, which I will explain in detail in the following subsections (42 U.S. Code § 262(k)).

2.2.1 Development Step 1: Discovery/Analytics

Before manufacturing on a large scale, companies and/or researchers must determine the compounds that have the best promise for having beneficial effects on various conditions. This is also called the analytical stage of development, as per Figure 2 (Cohen, 2019). For the creation of a new biologic drug, researchers test thousands of compounds until a few are determined to be effective enough for further study (Office of the Commissioner, n.d.). These candidates are then tested to determine parameters such as metabolization, interaction with other drugs, drug

delivery method, and dosage (Office of the Commissioner, n.d.). Once all necessary parameters have been determined, further testing can begin.

In the case of biosimilars, analytical evaluation is needed to show that the drug is similar to the reference biologic (Biosimilar Resource Center, n.d.). These studies need to show that the biosimilar has both a structural and functional match to the reference, which is tested using multiple bioassays that measure structure, protein content, thermal stability, and other factors (Cohen, 2019). While more emphasis is placed on this stage during biosimilar development, the tests conducted in this stage of development are done on a small scale. This means that they are not as expensive or time-consuming as later-stage testing typically required for a reference biologic (Cohen, 2019).

2.2.2 Development Step 2: Preclinical Trials

During the preclinical research phase, sometimes referred to as Phase 0, laboratories test the drug using both *in vitro* and *in vivo* methods. *In vitro* refers to running experiments outside of a living organism, while *in vivo* refers to running the tests on a living organism, also referred to as animal testing (MPKB, n.d.). These studies are completed to further determine the correct dosage and toxicity before moving to human subject testing. If the drug is determined to be safe enough, larger trials begin (Office of the Commissioner, n.d.). When ready to move on from this development step, manufacturers must submit an Investigational New Drug Application (IND), which the FDA must approve before human trials can commence (Office of the Commissioner, n.d.).

Again, more emphasis is placed on this stage for biosimilar development than it is for the development of a reference biologic. During this stage, biosimilar manufacturers must show that their drug has highly similar toxicity results to that of the reference (Dabrowska, 2019). This

type of testing is again less time-consuming and costly than later-stage human testing, further simplifying the process for biosimilar creators.

2.2.3 Development Step 3: Clinical Trials

Clinical trials are studies conducted on people to learn how a drug will interact with the human body. Researchers decide who participates in the study, the length, and what specific data will be analyzed (Office of the Commissioner, n.d.). There are also different phases of clinical trials, each building on top of the other. Phase I studies the drug in a small group of under 100 people to further learn about safety and identify side effects (USDHHS, 2017).

After the drug is determined to be safe enough, the trials move to Phase II. In this phase, the drug is given to a larger group of participants to determine effectiveness and therapeutic dosage (USDHHS, 2017). In Phase III, there are typically up to 3,000 subjects participating in the study which lasts up to four years (Office of the Commissioner, n.d.). During this phase, the efficacy and side effects continue to be monitored. Additionally, researchers compare the results to similar treatments (HSDHHS, 2017).

These clinical trial steps are represented as the two bars closest to the top of Figure 2, which are of the most importance for reference biologics, and less importance for biosimilars. Reference biologics are required to go through all three phases of clinical trials since they are a new drug and must be tested completely prior to approval. Biosimilars must also enter Phase I clinical trials to show that the intended effects of the drug are similar to that of the reference (Cohen, 2019). However, biosimilars typically do not enter Phase II trials. This is because the dosage will be the same as the reference drug because of their similarity, and therefore does not need to be tested extensively (Dabrowska, 2019). Biosimilars then enter Phase III clinical trials to confirm that the dose is effective and the drug continues to be safe (Cohen, 2019).

Starting with the IND application, the FDA becomes more heavily involved during these phases. During clinical trials, companies must comply with Good Laboratory Practices (GLP) and Good Manufacturing Practice (GMP) regulations. These regulations ensure that everything is documented (Center for Drug Evaluation and Research, 2018). Additionally, the FDA has the right to visit clinical trial data collection sites to observe. These regulations keep companies on track with both documentation and patient safety, because if the FDA discovers something unacceptable, the drug will not get approved and the money invested in research will be lost. The FDA involvement is the same for both biosimilars and their reference products to ensure safety and efficacy.

2.2.4 Development Steps 4 and 5: Review and Post-Market Monitoring

Once a company concludes its clinical trials, it must file a Biologics License Application (BLA) to begin the FDA review process. These applications include all the data associated with the drug, from discovery through clinical trials. Multiple FDA committees examine the data and determine if it is sufficient. While one team reviews data for patient safety, another looks for the maintenance of GLP, and so on. There is overlap within all of these committees, which means all of the data for a drug is thoroughly reviewed. If all committees are in agreement that the new drug is safe and effective, it is approved for market (Office of the Commissioner, n.d.).

While the BPCIA provides the incentive of streamlined development throughout the process for biosimilars, reference biologics manufacturers only begin to experience incentives after a BLA is filed. Under the BPCIA, biosimilar companies are required to inform the reference company when they file a BLA. Using the “patent dance” process outlined by the BPCIA, the two companies are then able to work out any patent disputes before FDA approval. By litigating any issues before approval, it allows biosimilars to remain on the market once they

are approved and provides reference manufacturers with settlement payouts (Calvo & Shea, 2020). The other incentive of 12-year market exclusivity for original biologics is granted during this time, when the FDA approves the BLA, giving those companies time to collect revenue without competition (U.S. Department of Health and Human Services et al, 2015a).

The final stage of development occurs after the product is released on the market. Drug manufacturers conduct post-market monitoring, sometimes considered a Phase IV clinical trial, to ensure safety and efficacy remain the same. Additionally, further testing and approval must be done if manufacturers want to change labels, update dosing, or add improvements (Office of the Commissioner, n.d.)

3 A REVIEW OF THE LITERATURE ON PHARMACEUTICAL INNOVATION AND THE BPCIA

Existing research mainly focuses on the FDA's specified goals for the BPCIA: "to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition" (U.S. Food and Drug Administration, 2019). Original biologic and biosimilar manufacturers are under the reach of the BPCIA. Biosimilar manufacturers have the incentive of a simpler approval process, while original biologics companies receive exclusivity rights. Both incentives are in place to encourage companies to produce more new drugs; increased creation of new products is innovation (Grabowski et al., 2014). More production of drugs leads to greater FDA approvals of biologics and biosimilars, which is an indicator of innovation. Approval of more drugs creates competition because there is a larger number of drugs on the market, resulting in better access and lower cost to patients (Grabowski et al, 2014; Singh & Bagnato, 2015).

Since its enactment in 2010, researchers have been studying the outcomes of the BPCIA to determine if its goals have been met and if changes need to be made to the legislature. Much of the literature focuses on two main subjects: patient accessibility and cost (Grabowski et al., 2011; Grabowski et al., 2014; Lyman et al., 2018; Mulcahy et al., 2018; Singh & Bagnato, 2015). While assessing these subjects is necessary when analyzing the BPCIA, both rely on a single precursor: innovation. The FDA aims to meet the BPCIA's goals "through competition," which can only occur if companies are innovating and having more products approved (U.S. Food and Drug Administration, 2019). However, few scholars have investigated the effects the BPCIA has had on innovation (Addivinola, 2018; Shepherd, 2015). This makes pharmaceutical innovation an important subject to investigate, as there is only a small amount of related existing research.

3.1 GAPS IN THE BPCIA

Despite the relatively simple process and outcomes the FDA suggests for the BPCIA, the existing research provides commentary that suggests otherwise. Some studies suggested areas for improvements to the BPCIA, leading the FDA to draft new guidance documents to clarify the process.

3.1.1 COST AND ACCESSIBILITY

When determining the success of the BPCIA, cost and accessibility are the typical metrics that researchers study because data is more accessible. Grabowski et al., 2011 estimated a savings of up to 40% for biosimilars, leading to an estimated $25-54 billion saved during the years 2014-2026 (Grabowski et al., 2014; Mulcahy et al., 2018). These results were based on a study of the Hatch-Waxman Act, which concluded generic drugs saw a discount of 40-80%, suggesting that the BPCIA may not be as impactful (Grabowski et al., 2011).

Patient accessibility is directly related to the cost of a drug; a lower price provides patients with a more affordable treatment option. However, multiple studies have identified potential problems with accessibility: provider reluctance and the biosimilar "interchangeable" classification (Grawboski et al., 2014; Lyman et al., 2018; Singh & Bagnato, 2015). Biosimilars are relatively new, and many physicians do not have enough knowledge of them to feel confident prescribing them, meaning they will continue to prescribe the original biologic (Lyman et al., 2018; Singh & Bagnato, 2015). Additionally, pharmacies cannot substitute the biosimilar for the original biologic unless the biosimilar has an "interchangeable" classification denoted by the FDA (Grabowski et al., 2014).

3.1.2 INNOVATION

The United States Department of Health and Human Services (2020) defines innovation as the increased output of new products to maintain market standing. In the case of pharmaceuticals, this means the output of new drugs. While there has been research on innovation in the pharmaceutical industry, most relies on theoretical analysis or is not specific to biologics. Innovation is harder to measure than other metrics such as cost, which is likely the reason not as much relevant research has been done.

A large portion of the discussion surrounding pharmaceutical innovation focuses on time and money (Shepherd, 2015; Singh & Bagnato, 2015). It takes both a tremendous amount of time and money to bring a new drug to market, which means it takes longer for a company to make back their money invested in R&D on a drug once it has been approved (Munos & Chin, 2011). Therefore, companies are more likely to focus on getting additional approvals for drugs they already have on the market, such as additional delivery methods or for use in the treatment of a new condition. While the work towards these additional approvals is innovative, it is not the type of breakthrough innovation needed.

Congress approved the Hatch-Waxman Act to promote innovation; this is the same goal for the BPCIA. Prior to its passage, only 19 percent of prescriptions were filled with generics, but as of 2019, almost 90 percent of prescriptions are filled with generics (Wilbur, 2019). This means that companies were creating new drugs, both original and generic. The Hatch-Waxman Act was successful at promoting innovation because of its provisions to protect generic companies from patent infringement and provide patent term restoration (Schact & Thomas, 2012).

Since the BPCIA is modeled after the Hatch-Waxman Act, it can be expected that the outcomes regarding innovation will be similar. However, creating drugs today is much different than it was in 1984; the pathway and incentives that worked back then will not work now. Because biologics and biosimilars are so much more complex than chemical drugs, the approval pathway is still a long and intensive process, despite the passing of the BCPIA (Singh & Bagnato, 2015).

Researchers hypothesize that the policy provisions contained within the BCPIA discourage innovation instead of promoting it (Blackstone & Fuhr, 2012; Shepherd, 2015). While the 12-year exclusivity period is great for original biologics manufacturers, this long period discourages companies from producing biosimilars (Shepherd, 2015). Additionally, original biologics companies spend time and money in efforts to thwart biosimilar companies' efforts to enter the market; they work on maintaining their "monopoly" on a specific drug rather than working to create new ones (Shepherd, 2015). While the BPCIA does include a patent resolution process, it is still vague and needs improvement (Blackstone & Fuhr, 2012).

Very few scholars have examined BPCIA outcomes empirically; empirical studies are important as they aid in tracking policy effects over time. Addivinola (2018) aimed to "analyze the impact of the BPCIA and its market exclusivity protections on biopharmaceutical innovation" by using clinical trial and drug approval data. He additionally tracked clinical trials and drug approvals after two other milestones—the European biologics pathway of 2004 and in 2007 at the start of negotiations for a biosimilars pathway in the US—to use as controls. Addivinola (2018) found that overall, the number of clinical trials rose following the enactment of the BPICA, which suggests the goal of innovation was achieved. However, industry-funded clinical trials significantly decreased from 480 to 392 trials per year after BPCIA enactment,

whereas institutionally funded clinical trials insignificantly increased from 157 to 189 trials per year (Addivinola, 2018). Addivinola (2018) hypothesized that this is because biopharmaceutical companies now also had to sort through regulatory and exclusivity burdens, whereas academic institutions did not.

Addivinola's analysis of BLA approvals is inconclusive because he did not have enough data to analyze a measurable response (2018). This is because, at the time of his research, not enough time had passed for a significant number of biologics and biosimilars to be approved. Addivinola (2018) concluded that there was an increase in pharmaceutical research and development following BPCIA enactment, meaning the BPCIA's objective of promoting innovation is fulfilled, despite being unable to establish absolute certainty of causality. This innovation is more so due to the work of original biologics manufacturers because biosimilar companies face more obstacles with exclusivity. Without the influx of biosimilars, the BPCIA's other goals of price reduction and increased accessibility may not be achieved (Addivinola, 2018; Margolis, 2013). Addivinola (2018) proposed that more research is needed in the future once more data becomes available and uncertain aspects of the BPCIA are clarified by the FDA.

3.2 Policy Modifications and FDA Guidance

Multiple researchers have noted that the long exclusivity periods and confusing patent litigation process within the BPCIA may be detrimental to fostering innovation (Blackstone & Fuhr, 2012; Shepherd, 2015). Additionally, there is a general lack of understanding about biosimilars by both physicians and patients (Lyman et al., 2018; Singh & Bagnato, 2015). In response, the FDA began releasing "Q&A" documents on the BPCIA in 2015, releasing an updated document every few years as new questions arose (Wilmot, 2019). This document answers questions regarding biosimilarity and interchangeability, requirements for BLA

submission, and exclusivity (New and Revised Draft Q&As, 2018). Additionally, the FDA released a "Biosimilars Action Plan," to explain how they planned on balancing the innovation and competition the BPCIA promised (Biosimilars Action Plan, 2018).

In 2019, the Biologic Patent Transparency Act (BPTA) was proposed to "increase transparency and reduce barriers that discourage efforts to bring generic alternatives to market" (*Bipartisan Group of Senators*, 2019). This bill proposed adding additional steps to the "patent dance" to provide better notice of BLA applications and patents to manufacturers, which would speed up litigation processes (Ainsworth & Watt, 2019). It also proposed requiring an updating of the Purple Book database to an easily searchable list and to include relevant patents (Ainsworth & Watt, 2019; *Bipartisan Group of Senators*, 2019). While the passage of this bill in late 2020 has fostered the creation of a searchable Purple Book, the patent list is only partially available through the Purple Book (S.659, 2019).

3.3 SUMMARY OF LITERATURE REVIEW FINDINGS

While there are many studies detailing the effect of BPCIA, it is difficult to draw definitive conclusions on its success because of the relative newness of the act. Studies show that while there may be reduced costs and increased innovation due to the BPCIA, some of its provisions, such as the patent litigation process, may also hinder more successful outcomes (Addivinola, 2018; Gabrowski et al., 2011; Shepherd, 2015). The literature shows that the BPCIA has complex impacts that need to remain in a balance to reach ideal outcomes.

The path diagram in Figure 3 describes the relationships that exist between the mechanisms and outcomes of the BPCIA. While the incentive of faster approval promotes the innovation of biosimilars, the long exclusivity period and patent disputes with biologic companies discourage it. Again, incentives promote original biologic innovation, but companies

still spend time protecting their data in patent disputes rather than creating new drugs. While research suggests that more drugs are being created, there is likely less innovation occurring than what is possible (Addivinola, 2018). After a drug is approved, there can only be market competition if new biologics and biosimilars are also entering the market—otherwise, patients will not see cost savings. Similarly, provider reluctance to prescribe biosimilars also hinders accessibility to these drugs. However, these final outcomes rely on companies innovating new products, and would otherwise not occur. While there has been some guidance documents and modifications to the BPCIA since its passage, they have only become available recently.

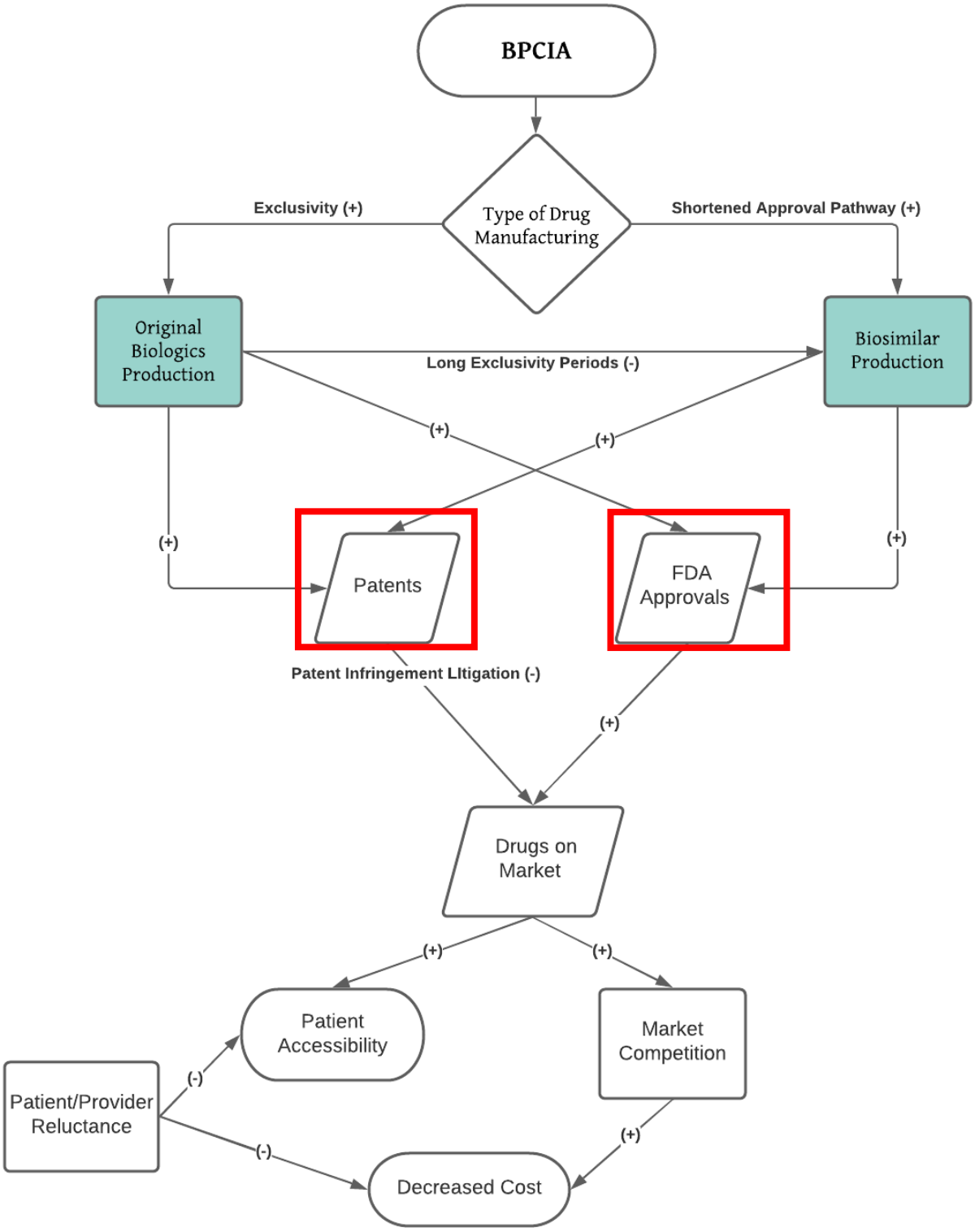

Figure 3. Actual outcomes of the BPCIA. Shaded blocks indicate where innovation should be occurring, and red squares where innovation can be measured. A (+) indicates a positive relationship, while a (-) indicates a negative one.

3.4 RESEARCH GOALS

The BPCIA was created to streamline approval for biosimilars and provide incentives to biologics manufacturers to promote innovation and provide more cost-friendly treatment options to patients. Current research suggests that it may be successful at reducing cost and increasing innovation, but there is a distinct lack of evidence to definitively conclude the BPCIA is successful. Most experts focus on cost and accessibility, utilizing comparisons to the Hatch-Waxman Act or trends within the entire pharmaceutical industry for their research (Grabowski et al., 2011; Grabowski et al., 2014; Mulcahy et al., 2018). Few researchers focus on the impact the BPCIA has had on innovation, and those that have only speculate that the provisions for exclusivity and patent litigation may have a negative impact on some outcomes (Blackstone and Fuhr, 2012; Shepherd, 2015). Addivinola (2018) is the only scholar to directly analyze pharmaceutical innovation regarding the BPCIA. However, he could not definitively conclude that there was a significant increase in innovation and suggested more research is required (Addivinola, 2018).

Given the lack of literature investigating the BPCIA's impact on innovation, this area of research needs more investigation. I hypothesize that the BPCIA may have mixed outcomes because of the multitude of both positive and negative interactions that occur in its pathway. Therefore, this thesis aims to empirically analyze the impact the BPCIA has had on biopharmaceutical innovation using drug approval and patent data.

4 METHODS

4.1 DATABASE SELECTION

The objective of this research is to measure innovation regarding the BPCIA by using publicly available data. There are multiple measures of technological innovation pertaining to biopharmaceuticals, including company R&D expenditures, drug approvals, clinical trials, and patents (Addivinola, 2018). The first step in gathering data is to determine which markers would be most useful for this analysis.

4.1.1 REJECTED DATABASES

Most pharmaceutical companies release annual budget reports, which include their R&D spending. It is logical to assume that if a company spends increasingly more on R&D over time that innovation is occurring. However, these reports do not specify what type of R&D is occurring. It is likely that the money is allocated to multiple different projects within the company and may not solely be used on biologics. Additionally, there is no database containing budget reports for all companies, which makes R&D spending an inadequate data source for this analysis.

Clinical trials are another marker of innovation; if a company has developed a potential biologic it must go through clinical trials before being approved by the FDA. If a company is conducting more clinical trials, it is likely working to produce more new biologics. The National Institutes of Health (NIH) maintains an online database of all registered clinical trials in the world. However, clinical trials are not only needed for new drugs. Each time a company wishes to market its drug for a different condition, clinical trials must be completed.

For example, the FDA first approved Abbvie's Humira (adalimumab) for the treatment of rheumatoid arthritis. Since then, Humira has also been approved for the treatment of chronic plaque psoriasis, Crohn's Disease, and other conditions (Abbvie, n.d.) The clinical trials for these subsequent approvals are not markers for new drug innovation. The structure of the clinical trials database makes it difficult to distinguish which trials are for new biologics, rendering this second source unsuitable for this analysis.

4.1.2 Selected Databases: FDA and USPTO

Drug approvals can also be used to track innovation. An increasing rate of drug approvals indicates that companies are innovating more pharmaceuticals. Every time a drug is approved, the FDA logs it into a database. The FDA has two databases to log drug approvals. The first is the "Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations," which contains information for all chemical/small molecule drugs approved by the FDA. This database has been in an online searchable format since 2005 (Center for Drug Evaluation and Research, 2020). At the beginning of 2020, the FDA released a second searchable database, the "Purple Book: List of FDA-Licensed Biological Products." This database is modeled like the Orange book and contains information on all biological products (Hahn, 2020). Both databases contain pertinent information such as approval date, applicant company, approval pathway, and prescriber information.

The amount of information provided by the FDA in these databases, in addition to the easily searchable and extractable format, make the Purple Book and Orange Book good data sources for this analysis. However, they only capture drugs that have already been approved and not those in development. To capture a bigger picture of the potential innovation occurring in the pharmaceutical industry, I need to include another source of data.

Patenting helps to track pharmaceuticals that are still in development. Companies will patent certain discoveries or processes throughout the drug development process, making it a good marker of innovation. Like the FDA databases for drug approvals, the United States Patent and Trade Office (USPTO) maintains a database of all approved US patents dating back to the late 18th century (USPTO, n.d.). The database allows the user to search based on specific criteria such as inventor, patent number, or assignee. The extent of the exported information is also chosen by the user. This customizability makes the USPTO database a good second source of data for this analysis.

4.2 Data Collection and Analysis

I restricted the data collected to an approximately 20-year time frame centered around the BPCIA enactment in 2010. This time frame allows for analysis both before and after the act to determine any changes that occurred. Restricting the time frame to 2000-2019 also reduces the size of the data extracted to a manageable extent. I utilized different strategies to collect data from the FDA and USPTO databases, which I will further explain in Section 5.

After compiling both sets of data, I analyzed them using both descriptive statistics and regression analysis (Section 5). Analyzing the descriptive statistics for each data set allowed me to determine if any trends were indicating more innovation after the passage of the BPCIA. I conducted regression analysis to determine if these trends were statistically significant. The use of controls allowed me to determine if the innovation was due to the BPCIA or an external factor.

5 ANALYSIS AND DISCUSSION

5.1 FDA DATABASE EVALUATION

5.1.1 DATA COLLECTION

The Purple Book webpage allows for the user to search for a specific drug or export the entire database. In this case, I exported the entire database to Excel, which included information for every drug filed under a BLA or a New Drug Application (NDA) that was converted to BLA. When drugs are approved for subsequent uses as described in the Humira example, the same BLA number is used, creating duplicate entries. I removed duplicates so only unique BLA numbers existed, meaning each biologic drug is listed once in the dataset. I also removed unnecessary variables, leaving only those pertinent to my research, such as the drug name, applicant company, approval year, and biologic/biosimilar classification.

While this research focuses on biologics, I also used the count of small molecule drug approvals retrieved from the Orange Book Database to use as a control. Like with the Purple Book, I kept only relevant variables and removed duplicates to leave unique NDA numbers. Based on the selected time frame, I edited both datasets to remove entries approved before 2000 and after 2019.

5.1.2 ANALYSIS BASED ON COUNTS OF FDA APPROVED DRUGS

The first set of data presented here is descriptive statistics of biologic drugs (Purple Book) approved by the FDA over years 2000-2019. The approved biologics count includes biosimilars as well as original biologics. I utilized small molecule drugs (Orange Book) as a control group to show general drug approval trends over time. I expect that biologics approvals will increase at a faster rate as compared to chemical drug approvals after the BPCIA enactment

if it does have a positive impact on innovation. There should be little impact on the chemical drug approvals because the BPCIA pathway does not include them.

I constructed a dataset by compiling the number of biologic drugs and small molecule drugs approved by the FDA each year, using the Purple and Orange Books. I plotted these approvals to create a time trend, as seen in Figure 4. This makes it possible to compare yearly trends between both types of drugs. It is important to note that both chemical and biologic drug approvals may increase due to the new technologies produced and knowledge gained each year.

There are almost 40 times more chemical drugs approved yearly as compared to biologic drugs. This is due to a multitude of reasons. Chemical drugs are easier to make and therefore cost less money for companies to produce. Additionally, there is already a more established market with defined innovative pathways such as the Hatch-Waxman Act. Biologic drugs are complex and therefore more expensive to make; there is also less knowledge in this area of the field, so fewer companies are producing them.

Prior to the enactment of the BPCIA (2000-2009), there does not appear to be any trends in biologic drug approvals. The number of approvals stays relatively steady during these years. After its enactment in 2010, there is a three-year period before there begins to be a marked increase in biologic drug approvals. The drug development and approval processes explain this three-year span before an increased approval rate occurs: a biosimilar can take three to five years to be developed and approved and was only allowed beginning in 2010. However, there is also an increasing trend for chemical drugs. This increasing trend in approvals for both types of drugs provides evidence that the BPCIA may be promoting the creation of more new biologic drugs, but there may be other contributing factors.

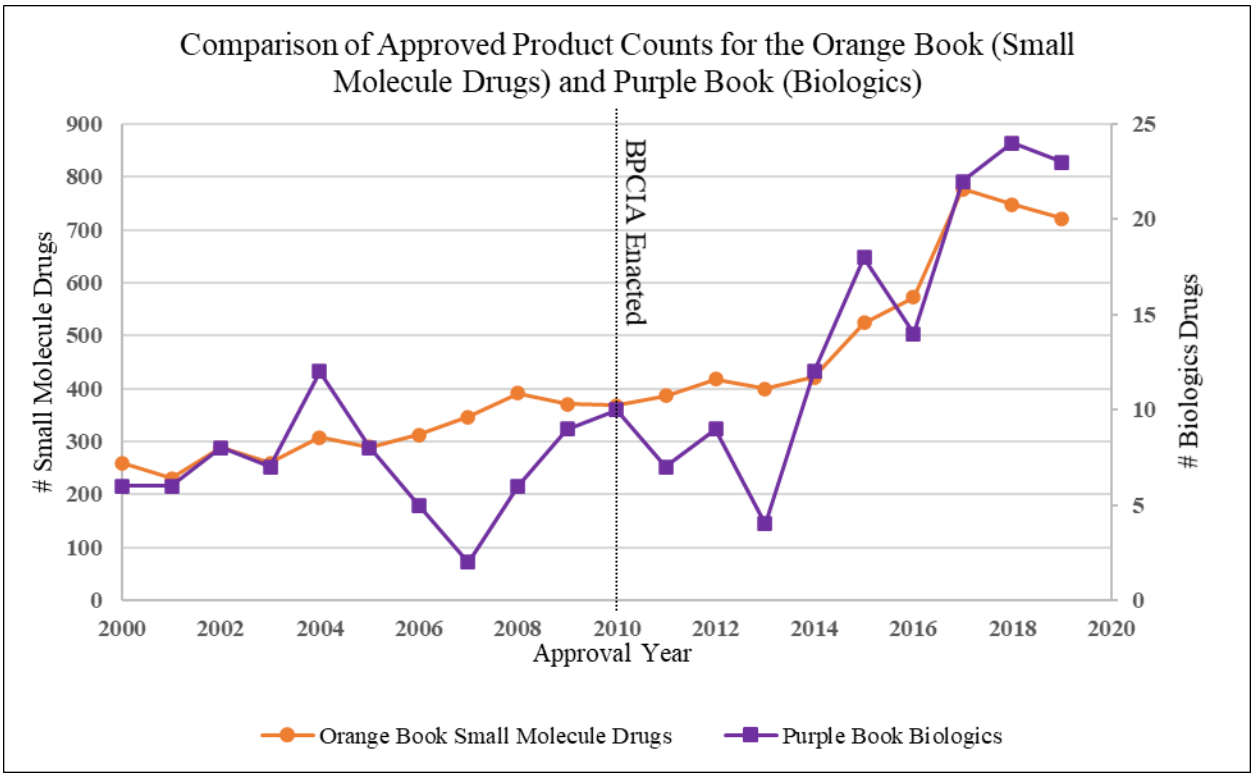

Figure 4. Comparison of Approved Products Counts for Small Molecule Drugs and Biologic Drugs 2000-2019

To look more closely at trends only related to biologic drugs, Figure 6 tracks approvals for biologics and biosimilar drugs.

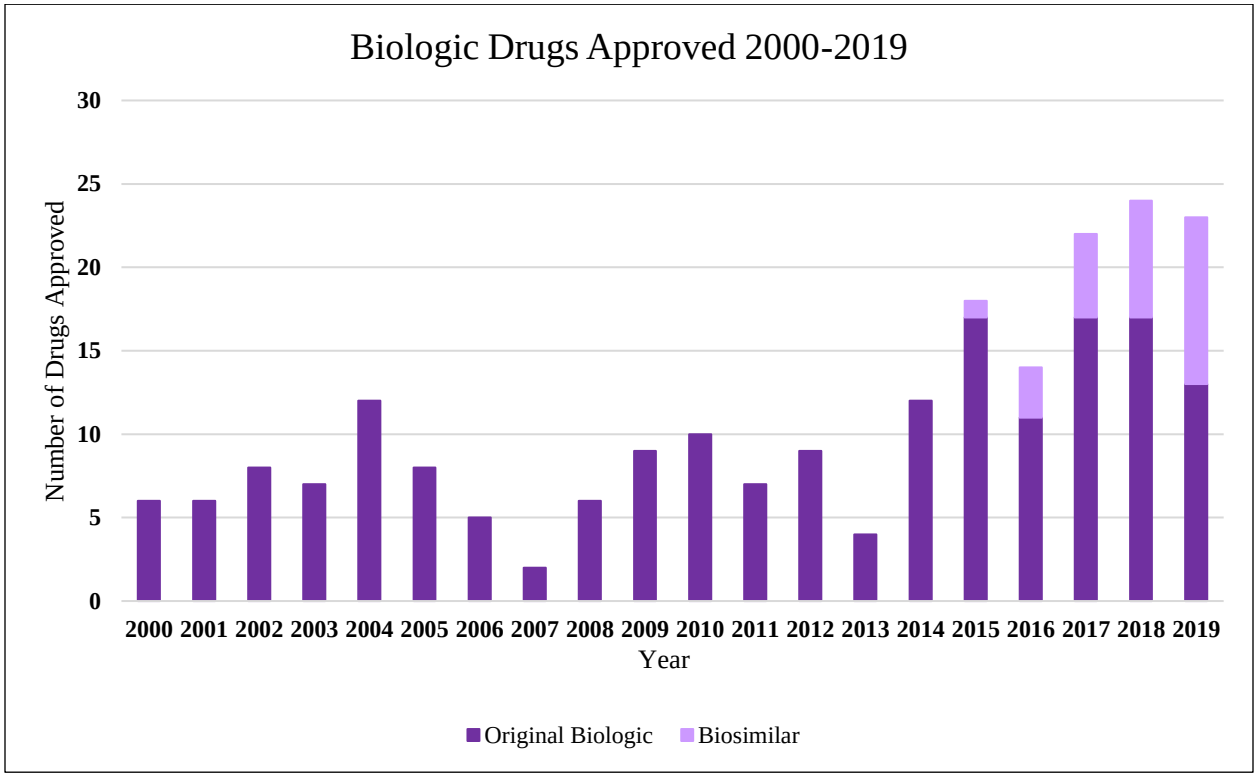

Figure 5. Approved product counts for biologics and biosimilar drugs 2000-2019

Figure 5 shows that the increase in biological drug approvals is dominated by original biologics. Approvals for biosimilar drugs began in 2015, with more biosimilar approvals occurring annually.

The trends within the count of the FDA-approved drugs may suggest an increase in biologic innovations after the 2010 BPCIA enactment, but do not provide tangible estimations of the innovation occurring in the biologics industry. A more complete analysis is necessary to fully estimate innovation.

5.1.3 Estimated Effects of BPCIA on Biologics Innovation Using Firm-Level Data

In addition to the yearly changes in the aggregate count of biologic drugs approved nationwide, I also examined the changes in such drug applications at the firm level.

To do this, I first merged the Orange Book and Purple Book databases into one. From here, I extracted a list of companies that filed applications for both biologics and small molecule drugs, producing a list of 56 firms (Appendix 1). With this list, I created a firm-level dataset, which includes the number of each type of drug approved annually for each company. I transformed this into a panel dataset, creating a single point for each firm per year, per type of drug. This allows for the control of unobserved time-invariant heterogeneity across the companies. With this data, I estimate the following model (Equation 1):

$$PB\_DRUG_{fy} = \beta_1 * POST2010 + \beta_2 * OB\_DRUG_{fy} + \eta_f + \varepsilon_{fy.} \quad (1)$$

In this model, the dependent variable is the number of biologic drugs (PB_DRUG) developed by firm *f* and approved by the FDA in year *y*. I use the number of small molecule drugs developed by firm *f* and approved by the FDA in year *y* as the control variable, OB_DRUG_{fy}. This dataset only includes the 56 firms that develop both biologic and small molecule drugs, so this variable should capture the overall innovativeness of a firm. However, firms may shift more resources to creating biologics after the enactment of the BPICA, so this coefficient, $\beta 2$, could be negative or positive. I created a dummy variable, POST2010, to identify the effect of the BPCIA. I coded the variable as one for years 2010-2019, and as zero for the years prior. The estimated coefficient is β_1, which should be a positive number if the policy does have a positive effect on innovation. This model also includes the firm-level fixed effects, η_f,

which control for the unobserved time-invariant firm-level characteristics. The error term is ε_{fy}. I estimated the model in STATA by clustering the standard errors at the firm level. Table 1 reports the results of my estimation.

Table 1. Estimated Effect of BPCIA on Firm-level Innovation of Biologic Drugs

	(1) OB Drug	***(2) PB Drug***	***(3) PB Drug***
POST2010	0.141 (0.256)	0.0839 *** (0.0293)	0.0837*** (0.0295)
OB DRUG	-	-	0.00158 (0.00706)
Constant	1.555 *** (0.128)	0.107*** (0.146)	0.105*** (0.016)
# Observations	1120	1120	1120
# of Firms	56	56	56
R-Squared	0.002	0.01	0.01

*Notes: In parenthesis are standard errors clustered at the firm level. All the specifications include firm-level fixed effects. *** p<0.01, ** p<0.05, * p<0.1*

In Column 1 of Table 1, I used the count of small molecules drugs as the dependent variable. The results show that the POST2010 dummy variable has a positive estimated coefficient, but it is statistically insignificant. This suggests that at the firm level, the BPCIA has little effect on small molecule drugs. In Columns 2 and 3, I used the count of biologic drug approvals as the dependent variable. Column 3 also includes the firm's approved small molecule drugs as the control, which directly estimates my model in Equation 1.

The estimated coefficient of the POST2010 dummy variable is positive and statistically significant in both columns, with a coefficient of approximately 0.1. This estimates that there is an average increase of 0.1 biologic drug approvals per company per year following the 2010

enactment of the BPCIA. This coefficient is small, indicating there is an increase of less than one drug approval per year. However, biologic and biosimilar drugs take multiple years for development, and less than a decade has passed since the BPCIA enactment. So, this coefficient suggests that while small, there has been a positive effect on biologics innovation.

These results appear to be in conflict with trends seen in Figure 4, which shows increasing counts of chemical and biologic drug approvals per years. However, my statistical evaluation was only based on a confined sample, firms that produce both types of drugs, rather than the whole population. By using the firm-level data, I was able to control for external factors that could affect innovation, unlike the data I examined within Figure 4.

One should note that the analysis of the FDA databases only covers a small part of what is considered innovation in the biologics sector. To further answer my research question, I looked at the USPTO database, which I previously determined was also a good source for tracking innovation.

5.2 USPTO DATABASE EVALUATION

As a company develops a drug, they typically submit patent applications for multiple inventions pertaining to a new drug. This can include a specific molecule that the company created, a new manufacturing process, or a storage solution for the final drug. This means that one approved drug can be associated with multiple patents.

For example, the company Abbvie created the biologic Humira, which was first approved in 2002. They submitted multiple patents related to Humira during its original development, as well as submitting more patents each time the company made an update to the drug. In total, Abbvie has 136 approved patents all related to the single drug Humira (Luthi, 2019).

In addition, patents for a biologic in development can be approved prior to FDA drug approval; the USPTO database can capture data on pharmaceuticals still in development, unlike the FDA database. Both this and the multiple patenting strategies create a larger, more detailed database than the FDA drug approvals.

5.2.1 USPTO DATABASE

The USPTO database is much vaster in comparison to FDA databases because it contains patents for all inventions in all industries. To make identifying patents easier, there are several coding schemes used to separate patents by type. The Cooperative Patent Classification (CPC) scheme is used by both the USPTO and European Patent Office (EPO), making these codes the most widely used.

A CPC code is comprised of numbers and letters denoting section, class, and group for a product type. Each subsequent part of the code makes it more specific. For example, CPC code A61K38/10 describes patents according to Table 2 below.

Table 2: Example of CPC code breakdown and definitions for A61K38/10.

Title	Scheme	Definition
Section	A	Human Necessities
Class	61	Medical or veterinary science; hygiene
Subclass	K	Preparations for medical, dental, or toilet purposes
Group	38	Medicinal preparations containing peptides
Subgroup	10	Peptides having 12 to 20 amino acids

To correctly identify patents relating to biologics, I first determined relevant CPC codes. To do this, I examined the Purple and Orange Books to identify a company that only created biologics drugs. In other words, a company that was only present in the Purple Book and not the Orange Book. I chose Regeneron Pharmaceuticals, Inc. as the company to investigate, as it has

more than one biologic on the market and no small molecule drugs. Using the PatentsView Advanced Search query tool, I conducted a search for Regeneron as an assignee, or the company behind the patent I exported the data to STATA, where I determined the most common CPC codes sorted by subclass (e.g. A61K).

To confirm that these were the proper codes, I conducted more searches for Alexion Pharmaceuticals and Dyax Corporation using the same methods as for Regeneron. I found that all the CPC codes overlapped, meaning the list determined from Regeneron's patents captures a large number of biologics-related CPC codes. I checked the most common CPC codes against the CPC patent dictionary to certify they are related to biologics. While determining the definitions of each code, I found that the specificity of subgroup was not needed. Instead, the main group code (A61K38 as per the example above), could be used, as all subgroups under it were relevant. This added hundreds more CPC codes to the list, making the search even more thorough. Additionally, most patents are identified using multiple CPC codes, making it likely that this list will capture most of the relevant patents. The final list of CPC codes used, and their definitions, is present in Appendix 2.

Using this list of CPC codes, I conducted more PatentsView Advanced Search queries based on the subclass code (C07K, A61K, C12N, G01N, and A61P). I only pulled records within the 2000-2019 timeframe. The relevant categories of assignee country, assignee organization, patent number, and patent approval date, in addition to the CPC data included in the data export. The data was then imported to STATA where only the group codes identified were kept. All of the datasets were merged, and any duplicate patents were dropped.

There are likely more relevant CPC codes than the ones chosen for identification of data in this analysis. However, since most patents are identified by multiple CPC codes, it is likely

that at least one of the CPC codes used is present on all biologics-related patents. Additionally, it is possible that the CPC codes could be used to identify inventions not related to biologics. This creates a margin of error that must be remembered during analysis.

5.2.2 Search Validity and Overlap with FDA Data

While I analyzed the selected databases separately, I must still compare them to determine if there is any similarity. Overlap between the two databases would provide evidence that patenting is a vital part of drug production and approvals. Having determined that there may be an increase of innovation in both patenting and drug development separately since the enactment of the BPICA, evidence that these statistics are related would provide further proof that innovation is occurring. If the databases contain widely differing data, then it would be more likely that innovation in at least one of the datasets may not be relevant to the BPCIA. Additionally, shared components between the two databases further prove that my methods for obtaining data and creating data sets are logical.

The two databases contain vastly different variables; however, they do both contain a variable for organization/manufacturer, which I can directly compare. I expect that the top companies in both databases will be highly similar, indicating that the previously determined innovation is related to the BPCIA. To determine if there is an overlap between the databases, I first created a list of the 15 top US-based patenting organizations. I then created a list of the same length for the top biologics manufacturers according to the Purple Book. I removed any foreign organizations from my top patenting list because the Purple Book only includes US-based manufacturers; the foreign organizations are not relevant in this comparison. It is important to note that these are the top patentors and manufacturers within the time frame 2000-2019. Changing or extending the period could yield different results.

I then compared these lists to determine if the same companies appeared on both. I additionally looked at the un-matched patenting organizations to determine if they appeared in the Purple Book in any capacity. The top 15 patentors and manufacturers are displayed in Tables 3 and 4 below.

Table 3. Top US-based patenting organizations 2000-2019

Assignee Organization	**Number of Patent Applications**
The Regents of the University of California	2182
Bristol-Myers Squibb Company	1971
Novartis	1754
Genentech, Inc.	1704
Hoffmann-La Roche Inc. (acquired Genentech in 2009)	1578
Merck Sharp & Dohme Corp.*	1500
Boehringer Ingelheim International GmbH*	1420
Allergan, Inc. (acquired by AbbVie in 2019)*	1375
Pfizer Inc.	1360
Janssen Pharmaceuticals	1242
The United States of America as represented by the Department of Health and Human Services	1178
AstraZeneca*	1037
Wyeth (acquired by Pfizer in 2009)	971
Amgen, Inc.	946
Eli Lilly and Company	893

*Note: Companies placed in **bold** appear in both the top patenting and top biologics lists. Organizations followed by an asterisk (*) are companies that have at least one biologic on the market, despite not being in the top 15 manufacturers. Subsidiaries and acquisitions are included and "counted" as the parent company if the transaction occurred within 2000-2019.*

Table 4. Top biologics manufacturers 2000-2019

Biologics Manufacturer	Number Biologics Approved
Genentech, Inc.	15
Amgen, Inc.	14
Sanofi-Aventis	10
Eli Lilly and Company	9
Novo Nordisk Inc.	9
Janssen Pharmaceuticals	6
Novartis	6
Pfizer Inc.	6
BioMarin Pharmaceutical Inc.	5
Bristol-Myers Squibb Company	5
EMD Serono, Inc.	5
Genzyme Corporation (subsidiary of Sanofi)	5
Sandoz Inc. (subsidiary of Novartis)	5
Alexion Pharmaceuticals, Inc. (acquired by AstraZeneca in 2020)	4
GlaxoSmithKline LLC (acquired Pfizer in 2019)	4

*Note: Companies placed in **bold** appear in both the top patenting and top biologics lists. All companies listed have filed at least one patent within the time frame. Subsidiaries and acquisitions are included and "counted" as the parent company if the transaction occurred within 2000-2019.*

These tables make evident that there is a large amount of overlap between the biologics-related top patenting and top manufacturing companies. Seven of the 15 organizations listed are top players in both sectors. However, within the pharmaceutical industry, there are frequently company merges and acquisitions, such as Pfizer's acquisition of Wyeth in 2009. These companies are listed separately because both filed patents and/or had drugs approved before combining. Additionally, most companies retain their name and are identified as a division of the parent company; for example, Wyeth is now "Wyeth, subsidiary of Pfizer, Inc".

When including these mergers, it increases the overlap of seven organizations to nine, meaning that 60% of the top patentors and manufacturers are the same. Of the remaining six top patenting organizations, all but two have at least one biologic drug approved. In retrospect, all remaining biologics manufacturers have at least one patent on file. The remaining two patenting

organizations appear to be outliers; they do not have any biologics drugs approved but have many relevant patents.

The first, The Reagents of the University of California, has the most patents filed overall. This is because the university focuses on the early research portion of pharmaceutical development, thus needing patents without getting drugs approved. The second outlying patenting organization is the Department of Health and Human Services, which does government-sanctioned research. Both organizations can license out patents and sell relevant research data to pharmaceutical companies. This saves pharmaceutical companies both time and money, as it can take the research and move directly into testing and development. The final product is then approved under the company name, with no mention of the main patenting organization. Likely, the top biologics manufacturers that do not have a high number of patents utilize this approach. For example, Sanofi-Aventis has a high number of biologics approved but does not appear within the top patentors.

5.2.3 Analysis Based on Counts of Patent Applications and Approvals

To begin evaluating the data collected from the USPTO database, I first constructed a dataset that has the number of patent applications and approvals each year related to biologics, using the dataset I created as described in Section 5.2.1. This data includes all relevant patent applications and approvals in the United States by both US and foreign companies. In line with the results I found during my analysis of the FDA database, I expect that there will be an uptick in both applications and approvals after 2010 if the BPCIA does promote more biologics innovation. I plotted this data to study its change over time, as seen in Figure 6.

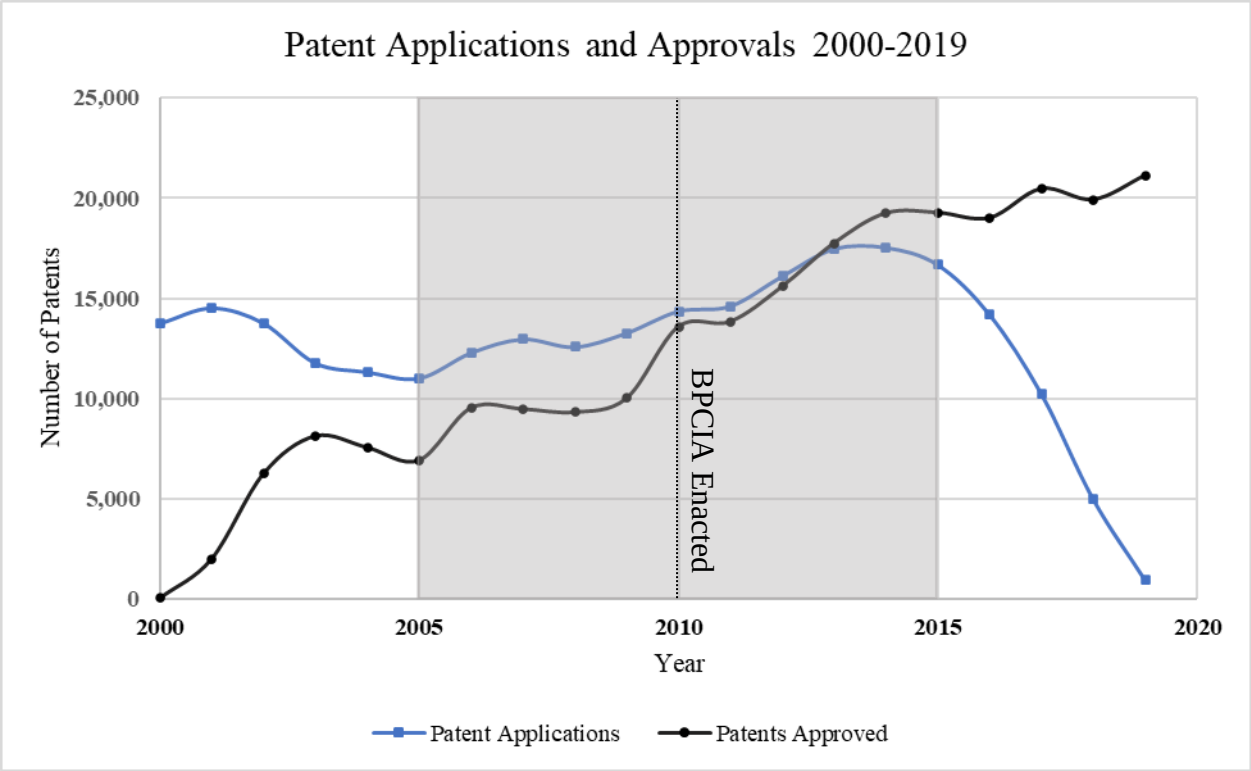

Figure 6. Comparison of patent applications and approvals in the United States during the 2000-2019 period

Note that the patent data is subject to a truncation issue because many of the recently submitted patent applications have not been approved yet and are thus not observed in the dataset. This is marked by a large decrease in patent applications after 2015. The results pulled from the main USPTO database only include patents that have been approved and publicized. Only the applications of these approved patents appear in the database. One can see a similar truncation issue with the approved patents before 2005. Only applications submitted beginning in 2000 were included in this search. This means that approved patents with application dates prior to 2000 are not reflected in this dataset.

Because of this truncation, the years before 2005 and after 2015 do not include the full amount of data available. Therefore, I only studied the patent data within the years 2005-2015

for this and all subsequent patent analyses. This change is reflected in Figure 7, which contains the same set of data as Figure B, adjusted to include only the non-truncated data. Figure 7 shows increasing numbers of both patent approvals and applications each year.

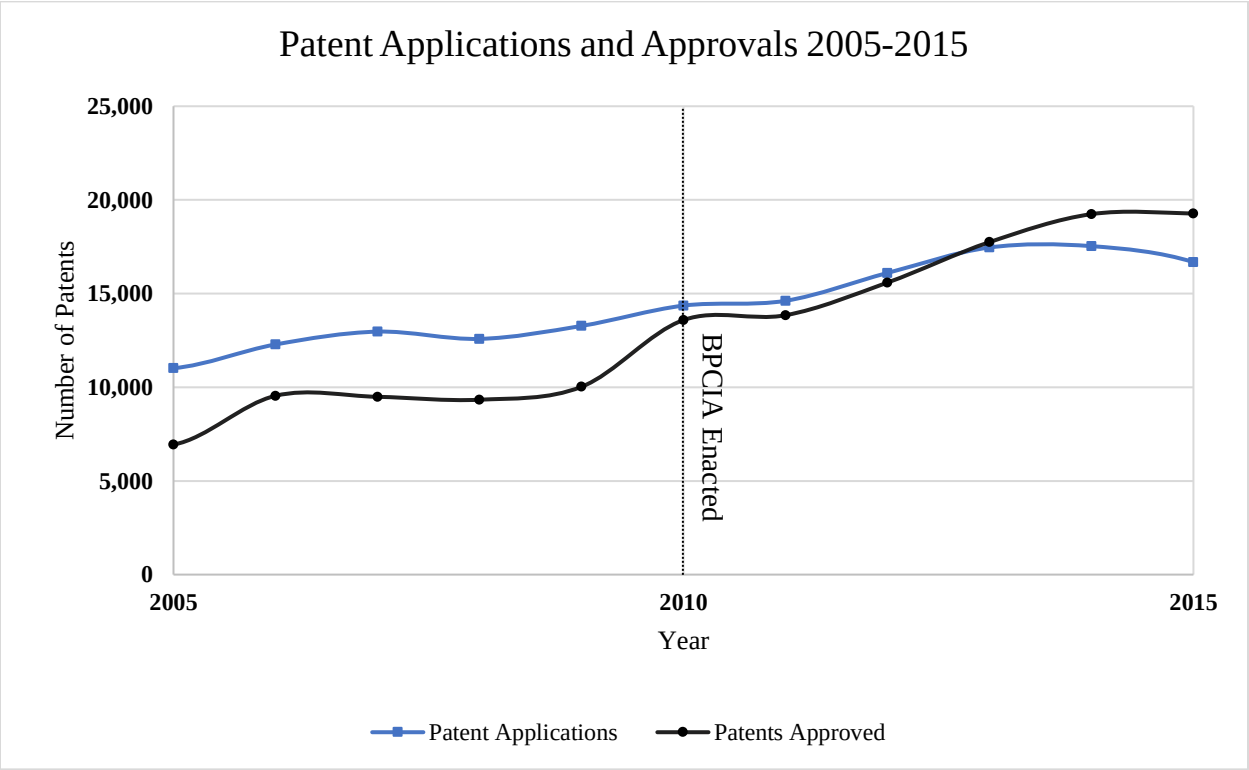

Figure 7. Patent Application and Approval Trends over Time, 2005-2015

It is important to note that this data includes patent applications/approvals from countries outside the United States. A company must patent their inventions in every country they want to market the product to protect their intellectual property. So, the data from foreign companies is included because they go through the same US patenting process as national companies. While non-US countries must follow the same patenting process, they may develop a product based on their own country's regulations. Only US-based organizations have had a biologic drug approved

by the FDA. To determine the patenting trends directly occurring from the BPCIA, I sorted the patent data by country.

5.2.4 Analysis of Patenting Trends for US-Based as Compared to Foreign Companies

Continuing with the same dataset, I created a list of all countries with their total number of biopharmaceutical patents. From here, I determined the five foreign countries that had the highest total patent counts for the years 2005-2015. These countries are Japan, Germany, China, Great Britain, and France. In this scenario, the foreign companies act as a control: they are not affected by the BPCIA and account for other external factors that can influence patenting.

I plotted the country-level patent data across two figures to study trends because there is a significantly higher number of US-based approvals as compared to foreign approvals. Figure 8-1 shows approvals for US-based patent applications over time and Figure 8-2 shows approvals for the other five countries.

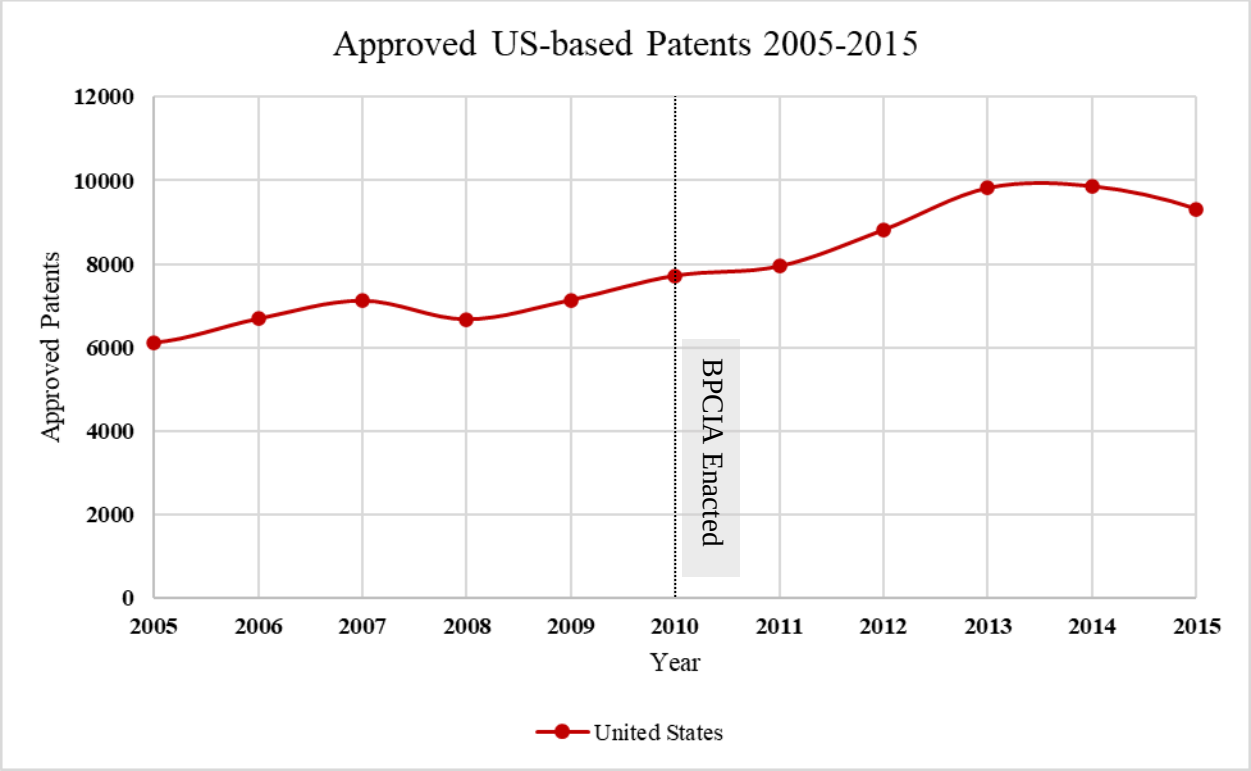

Figure 8-1. United States patent applications approved by the USPTO 2005-2015

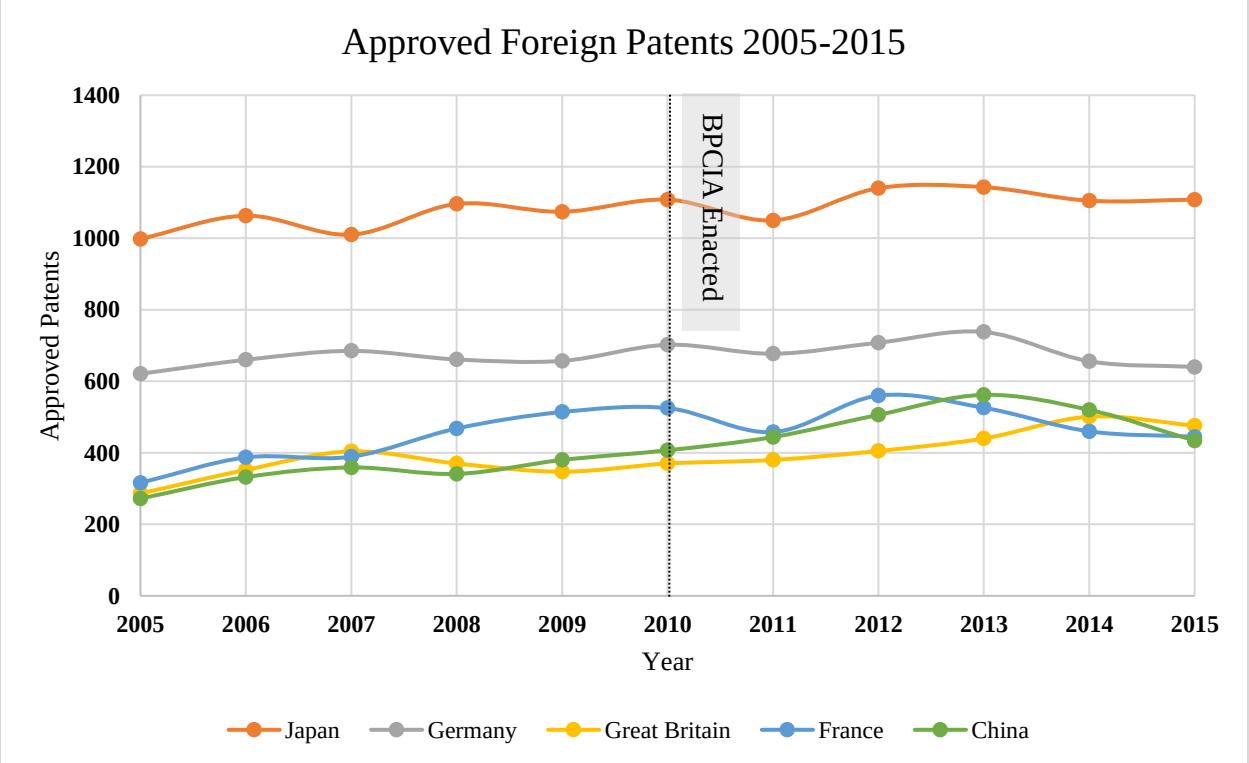

Figure 8-2. Foreign patent applications approved by the USPTO 2005-2015

The number of US-based patent approvals in Figure 8-1 increases across the entire ten-year span. However, after the 2010 BPCIA enactment, there appears to be a sharper increase in patent approvals. While there may be other contributing factors, the BPCIA likely also contributed to increasing innovation. In comparison, the number of annual foreign patents in all five foreign countries does not show significant change; they stay relatively constant over the ten-year period. This may suggest that biopharmaceutical innovations in foreign countries are unaffected by the BPCIA. If these foreign trends showed a steady increase over the entire ten-year span, it would be an indication that there is some other factor contributing to the rate of approvals, such as technological advances.

5.2.5 Estimated Effects of the BPCIA on US-Based Companies

I also estimated a difference-in-difference model to further examine the impact of the BPCIA on biopharmaceutical patenting trends in US-based firms compared to foreign firms. I constructed a balanced panel dataset of patent application counts by country by year. My sample includes a total of 18 countries (US included), which have filed at least 2,000 patent applications related to biologics between 2000 and 2019. Using this set of data, I estimated the following equation (Equation 2):

$$PATENT_{cy} = \beta_1 * POST2010 * US + \gamma_c + \eta_y + \varepsilon_{cy.} \quad (2)$$

In this model, the dependent variable is the number of patent applications (*PATENT*) filed by country *c* in year *y*. I again created a dummy variable, *POST2010,* to identify the effect of the BPCIA. I coded the variable as zero for the years prior to enactment and one for the years following. The independent variable (*US*) is coded as one for US-based firms and zero for

foreign firms. The coefficient β_1 estimates the policy impact on the count of applications filed by the US firms, as compared to foreign firms. This coefficient would be positive if the BPCIA has a positive impact on US-based biopharmaceutical patents. This model also includes the year-level fixed effects, η_y, and country-level fixed effects, γ_c. These variables act as controls and account for the advancement of knowledge and foreign policy over the years 2000-2019. Unlike my previously presented results, I used data from all years instead of 2005-2015. This is because my model includes the year-level fixed effects, which account for the truncation that occurs during the early and late years.

I estimated my regression model using STATA. The estimated coefficient, β_1 is 163.4, with a P value at 0.000. This result suggests that there is a significant increase of biologics applications filed in the US because of the policy. Since this model controls for year-level fixed effects and non-US countries, I can determine that this coefficient is only related to patenting trends within the United States.

6 CONCLUSIONS

6.1 SUMMARY OF FINDINGS

The Biologics Price Competition and Innovation Act provides pharmaceutical manufacturers incentives with the goal that their increased innovation will lead to better accessibility and lower cost to patients (U.S. Food and Drug Administration, 2019). This thesis aimed to study the outcomes of the BPCIA and determine if there has been an influence on innovation. To accomplish this, I conducted statistical analysis of drug approval and patent data collected from the FDA and USPTO, respectively. This study is one of the first to empirically analyze the effects of the BPCIA regarding pharmaceutical innovation, whose conclusions provide a basis for future researchers to work from.

The first set of analyses focused on the FDA approvals of original biologics and biosimilars. The number of biologics approved each year generally increased after 2010 BPCIA enactment, suggesting the pharmaceutical industry responded favorably to the new legislation. My research analyzing companies producing both biologic and chemical drugs indicates that there is a statistically significant increase of 0.1 biologics approvals each year following the BPCIA.

Biologics-related patent approvals composed my second set of analyses. The rate of US patent applications and approvals increased in the years following the BPCIA. Patents submitted by non-US entities did not increase after 2010, stipulating that only the BPCIA and not other factors is responsible for the US patent increase. Patent approvals from US-based companies increased at a rate of about 164 approvals per year after 2010.

Overall, my research shows that the BPCIA has had a positive impact on US-based pharmaceutical innovation. However, as evidenced by the literature review, the interactions between the BPCIA's outcomes may be limiting it from its full potential. Additionally, this does not allow me to fully categorize the BPCIA as a "success" or "failure." My study only measures innovation and does not estimate if it is enough to provoke a change in the other outcomes of accessibility and cost.

6.2 LIMITATIONS

There are several other limitations of this study. The data collected for this study relies only on what is publicly available through the FDA and USPTO databases. This data only captures approved biologics or approved patents, meaning some projects in development may not be captured. This is especially apparent when analyzing the patent data, as the data had to be truncated to a shorter period to account for patents that were still awaiting approval. Because the CPC codes used to collect the patent data were chosen based on their definitions, there is a chance that not all relevant CPC codes were chosen. However, many patents are categorized using multiple CPC codes, meaning the majority of relevant patents were most likely captured in my search.

Secondly, the BPCIA was only established in 2010, meaning only about a decade has passed with the policy in effect. In the pharmaceutical industry, this is a very small timescale, as it can take up to twelve years to develop and approve a biologic drug and up to ten years for a biosimilar (GBI Research, 2017). The period for which data was collected, 2000-2019, therefore only captures a limited view of the industry. To account for this, the patent data was also collected and analyzed to account for drugs that may still be in development.

Another limitation of this research is that I did not separate biologic and biosimilar drugs when conducting my statistical analyses studying drug and patent approvals. It is possible that the BPCIA impacts biosimilars innovation differently than biologics innovation. This is because the provisions for patent litigation and exclusivity periods within the Act affect them differently. My study does not produce results for them individually, but rather leaves them within the one overall category of biopharmaceuticals.

The biggest limitation of this study is the ability to determine a causal relationship between pharmaceutical innovation and the BPCIA. There are a vast number of variables that can influence the pharmaceutical industry, such as advances in technology and scientific knowledge, access to funding, or state of the economy and political climate. To overcome this challenge, I used chemical drug approvals to control for other influences that may have affected the pharmaceutical industry. For patents, I utilized foreign countries as a control, as they would be unaffected by the BPCIA. However, it is possible that there are other unobserved factors that may influence these measures over the study period after the BPCIA was enacted.

6.3 IMPLICATIONS OF FINDINGS

The BPCIA has successfully allowed biosimilars to enter the US market, but it is likely innovation could occur at a higher rate. Some provisions within the BPCIA are hindering it from reaching its full potential. Policymakers should continue to monitor industry response to the BPCIA and release new guidance if necessary.

More research is needed to determine the overall success of the BPCIA. It would be beneficial to re-visit this topic in ten or more years, as more data will be available and may indicate different outcomes. Future scholars may also study other indications of innovation, such as clinical trials data or R&D expenditures, to confirm my findings. A more extensive future

study could include an investigation of drug pricing in addition to innovation to measure the outcomes of the BPCIA more quantitatively.

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APPENDIX 1: FIRMS CREATING BOTH BIOLOGIC AND CHEMICAL DRUGS

Pharmaceutical Firm	# Biologic Drugs Approved	# Chemical Drugs Approved
Abbvie, Inc.	3	22
Aegerion Pharmaceuticals, Inc.	1	1
Akorn, Inc.	1	80
Amgen, Inc.	13	3
Amphastar Pharmaceuticals, Inc.	1	7
Astellas Pharma US, Inc.	2	9
AstraZeneca	2	32
Auxilium Pharmaceuticals LLC	1	2
Bausch and Lomb, Inc.	2	41
Baxter Healthcare Corp.	1	40
Biogen, Inc.	3	3
Biomarin Pharmaceutical, Inc.	5	1
Boehringer Ingelheim Pharma, Inc.	2	23
Bristol Myers Squibb Co	5	13
Celgene Corp	1	5
Celltrion, Inc.	3	11
Daiichi Sankyo, Inc.	1	9
Eli Lilly and Co	9	16
EMD Serono, Inc.	5	3
Ferring Pharmaceuticals, Inc.	2	8
Genentech, Inc.	15	5
Genzyme Corporation	4	7
GlaxoSmithKline	4	40
Hoffmann La Roche, Inc.	2	9
Horizon Pharma USA, Inc.	1	6
Hospira, Inc.	2	89
Insmed, Inc.	1	1
Ipsen Biopharmaceuticals, Inc.	2	2
Janssen Biotech, Inc.	6	30
Jazz Pharmaceuticals, Inc.	1	5
Kyowa Kirin, Inc.	2	2
Leadiant Biosciences, Inc.	1	1
Merck Sharp and Dohme Corp	3	37
Merz Pharmaceuticals, LLC	1	1

Pharmaceutical Firm	# Biologic Drugs Approved	# Chemical Drugs Approved
Mylan Pharmaceuticals, Inc.	2	436
Novartis Pharmaceuticals Corp	6	70
Novo Nordisk, Inc.	9	7
NPS Pharmaceuticals, Inc.	1	1
Organon USA, Inc.	2	4
Pfizer, Inc.	6	18
Pharmacia and Upjohn Co	1	5
Sandoz, Inc.	5	144
Sanofi Aventis US LLC	10	22
Schering Corp	1	2
Shire Development, Inc.	2	9
Spectrum Pharmaceuticals, Inc.	1	1
Sun Pharmaceutical Industries Ltd.	1	240
Swedish Orphan Biovitrum AB	2	1
Takeda Pharmaceuticals USA, Inc.	1	17
Teva Pharmaceuticals USA	2	244
UCB, Inc.	1	10
United Therapeutics Corp	1	3
Valeant Pharmaceuticals	1	17
Vifor, Inc.	1	1
Vivus, Inc.	1	1
Wyeth Pharmaceuticals LLC	2	4

APPENDIX 2: CPC CODES USED FOR PATENT SEARCH

Subclass ID	Subclass Definition	Subgroup ID	Subgroup Definition
C07K	PEPTIDES	C07K2317	Immunoglobulins specific features
		C07K16	Immunoglobulins [IGs], e.g. monoclonal or polyclonal antibodies
		C07K14	Peptides having more than 20 amino acids; Gastrins; Somatostatins; Melanotropins; Derivatives thereof
		C07K2319	Fusion polypeptide
A61K	PREPARATIONS FOR MEDICAL, DENTAL, OR TOILET PURPOSES	A61K2039	(same as A61K39)
		A61K38	Medicinal preparations containing peptides
		A61K39	Medicinal preparations containing antigens or antibodies
		A61K47	Medicinal preparations characterised by the non-active ingredients used, e.g. carriers or inert additives; Targeting or modifying agents chemically bound to the active ingredient
		A61K31	Medicinal preparations containing organic active ingredients
		A61K45	Medicinal preparations containing active ingredients not provided for in groups A61K 31/00 - A61K 41/00
		A61K9	Medicinal preparations characterised by special physical form
		A61K2300	Mixtures or combinations of active ingredients, wherein at least one active ingredient is fully defined in groups A61K 31/00 - A61K 41/00
		A61K49	Preparations for testing in vivo
C12N	MICROORGANISMS OR ENZYMES; COMPOSITIONS THEREOF; PROPAGATING, PRESERVING, OR MAINTAINING MICROORGANISMS; MUTATION OR GENETIC ENGINEERING; CULTURE MEDIA	C12N15	Mutation or genetic engineering; DNA or RNA concerning genetic engineering, vectors, e.g. plasmids, or their isolation, preparation or purification; Use of hosts thereof
		C12N2800	Nucleic acids vectors
		C12N5	Undifferentiated human, animal or plant cells, e.g. cell lines; Tissues; Cultivation or maintenance thereof; Culture media therefor
		C12N9	Enzymes; Proenzymes; Compositions thereof; Processes for preparing, activating, inhibiting, separating or purifying enzymes
		C12N2015	(same as C12N15)
		C12N2840	Vectors comprising a special translation-regulating system
		C12N2501	Active agents used in cell culture processes, e.g. differentation

Subclass ID	Subclass Definition	Subgroup ID	Subgroup Definition
		C12N2830	Vector systems having a special element relevant for transcription
G01N	INVESTIGATING OR ANALYSING MATERIALS BY DETERMINING THEIR CHEMICAL OR PHYSICAL PROPERTIES	G01N33	Investigating or analysing materials by specific methods not covered by groups G01N 1/00 - G01N 31/00
		G01N2333	Assays involving biological materials from specific organisms or of a specific nature
		G01N2500	Screening for compounds of potential therapeutic value
		G01N2800	Detection or diagnosis of diseases
A61P	SPECIFIC THERAPEUTIC ACTIVITY OF CHEMICAL COMPOUNDS OR MEDICINAL PREPARATIONS	A61P1	Drugs for disorders of the alimentary tract or the digestive system
		A61P11	Drugs for disorders of the respiratory system
		A61P13	Drugs for disorders of the urinary system
		A61P17	Drugs for dermatological disorders
		A61P19	Drugs for skeletal disorders
		A61P21	Drugs for disorders of the muscular or neuromuscular system
		A61P25	Drugs for disorders of the nervous system
		A61P27	Drugs for disorders of the senses
		A61P3	Drugs for disorders of the metabolism
		A61P31	Antiinfectives, i.e. antibiotics, antiseptics, chemotherapeutics
		A61P35	Antineoplastic agents
		A61P37	Drugs for immunological or allergic disorders
		A61P5	Drugs for disorders of the endocrine system
		A61P7	Drugs for disorders of the blood or the extracellular fluid
		A61P9	Drugs for disorders of the cardiovascular system