THE EFFECTS OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 ON BIOPHARMACEUTICAL RESEARCH AND DEVELOPMENT

A dissertation presented

by

Frank John Addvinola, Jr.

to

The School of Public Policy and Urban Affairs

In partial fulfillment of the requirements for the degree of

Doctor of Philosophy

In the field of

Law and Public Policy

Northeastern University
Boston, Massachusetts
March 2018
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ABSTRACT OF DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Law and Public Policy in the College of Social Sciences and Humanities of Northeastern University
March 2018
ABSTRACT

The biopharmaceutical industry is a significant and rapidly growing sector of the U.S. economy and is critical for tackling many diseases affecting large patient populations. The Biologics Price Competition and Innovation Act (BPCIA) was enacted by Congress in 2009 with the legislative intent to increase innovation and patients’ access to biopharmaceuticals by stimulating biotechnology research and development and lowering prices for patients. In this dissertation research, I analyze the impact of the BPCIA and its market exclusivity protections on biopharmaceutical innovation to influence new biological drug development. This study examines how selected indicators of research and development within the biopharmaceutical industry responded to the enactment of the BPCIA. I used published data and compiled time-series analyses to identify major shifts in selected metrics of biopharmaceutical innovation (i.e., indicators) in response to key events (i.e., milestones) associated with the emergence and enactment of the BPCIA. In my data analysis, I measure changes in indicators that mark increases or decreases in innovation activity within biopharmaceutical research and development that may have occurred in response to implementation of the BPCIA. Through this analysis of the BPCIA, I attempt to answer a broader question “Do legislative changes in market exclusivity protection affect innovation in biopharmaceuticals?” Answering this question will address the persistent public policy argument of whether stronger market exclusivity affects innovation and if so, whether the effects are positive or negative. Through interpretation of empirical evidence, my research supports the favorable linking of market exclusivity and encouraging innovation. However, the data analyses also show that biopharmaceutical industry is faced with many regulatory burdens placed by the BPCIA for the development of follow-on biosimilars, which may hinder the opportunities for future cost savings to patients.
A very special gratitude goes out to my dissertation advisor, Professor Thomas H. Koenig, who guided me through this research and writing for his patience and support in overcoming numerous obstacles I have been facing though my research.

I would like to thank the members of my committee, Professor Stephen Y. Chow and Professor Gregory H. Wassall, for their valuable and helpful input that helped me make this work better.

Also, I would like to thank the faculty, staff and graduate students at the Department of Law and Public Policy at Northeastern University for the gratifying learning and teaching experience I was enriched by during the years leading to this dissertation research.
DEDICATION

This dissertation is dedicated first and foremost to my loving wife, Angelica Elle Addvinola. I am forever grateful for your support and encouragement. You gave me more than your love and support. You have helped me become a better writer, a better scholar, and a better person.

I also dedicate this work to my son, Frank J. Addvinola, III. who recently joined our family and brought light and joy into our home.

This work is also dedicated to my late father, Frank J. Addvinola, Sr. who instilled in me the value of education, learning and self-improvement.

Finally, I would like to dedicate this work to thousands of devoted biotechnology scientists who commit their lives to the discovery of cutting-edge technologies that help ameliorate and cure debilitating diseases and save human lives.
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<tbody>
<tr>
<td>ACA</td>
<td>Affordable Care Act, aka Patient Protection and Affordable Care Act (2010)</td>
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<td>ACT</td>
<td>Applicable Clinical Trial</td>
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<td>ANDA</td>
<td>Abbreviated New Drug Application</td>
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<td>BIO</td>
<td>Biotechnology Industry Organization</td>
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<td>BLA</td>
<td>Biologic License Application</td>
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<tr>
<td>BPCIA</td>
<td>Biologics Price Competition and Innovation Act (2009)</td>
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<td>CBO</td>
<td>Congressional Budget Office</td>
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<td>CDC</td>
<td>Center for Disease Control</td>
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<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
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<td>CFR</td>
<td>Code of Federal Regulations</td>
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<td>CGMP</td>
<td>Current Good Manufacturing Practice</td>
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<td>DIA</td>
<td>Drug Information Association</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<td>GPhA</td>
<td>Generic Pharmaceutical Association</td>
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<td>ELA</td>
<td>Establishment License Application</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EMEA</td>
<td>European Medicines Evaluation Agency</td>
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<td>EU</td>
<td>European Union</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FDAAA</td>
<td>Food and Drug Administration Amendments Act (2007)</td>
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<td>FDAMA</td>
<td>Food and Drug Administration Modernization Act (1997)</td>
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<td>FDCA</td>
<td>Federal Food, Drug, and Cosmetic Act (1938)</td>
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<td>FOB</td>
<td>Follow-on biologic</td>
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<td>FR</td>
<td>Federal Register</td>
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<td>FTC</td>
<td>Federal Trade Commission</td>
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<td>GATT</td>
<td>General Agreement on Tariffs and Trade (1986)</td>
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<td>HHS</td>
<td>Health and Human Services</td>
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<td>H.R.</td>
<td>House Resolution</td>
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<td>IND</td>
<td>Investigational New Drug</td>
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<td>IP</td>
<td>Intellectual Property</td>
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<td>IPR</td>
<td>Intellectual Property Regulations</td>
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<tr>
<td>L.L.C.</td>
<td>Limited Liability Company</td>
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<td>NCE</td>
<td>New Chemical Entity</td>
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<td>NCHC</td>
<td>National Coalition on Health Care</td>
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<td>NDA</td>
<td>New Drug Application</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>Abbreviation</td>
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<tr>
<td>NME</td>
<td>New Molecular Entity</td>
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<td>ODA</td>
<td>Orphan Drug Act (1983)</td>
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<td>OTC</td>
<td>Over-the-Counter Drugs</td>
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<td>PCMA</td>
<td>Pharmaceutical Care Management Association</td>
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<td>PDUFA</td>
<td>Prescription Drug User Fee Act (1992)</td>
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<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
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<td>PHS</td>
<td>Public Health Service</td>
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<td>PHSA</td>
<td>Public Health Service Act (1944)</td>
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<td>PLA</td>
<td>Product License Application</td>
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<td>PMA</td>
<td>Pharmaceutical Manufacturers Association</td>
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<td>PPACA</td>
<td>Patient Protection and Affordable Care Act, aka Affordable Care Act (2010)</td>
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<td>R&amp;D</td>
<td>Research and Development</td>
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<td>RLD</td>
<td>Reference Listed Drug</td>
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<td>S&amp;P</td>
<td>Standard and Poor</td>
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<td>SOP</td>
<td>Standard Operating Procedures</td>
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<tr>
<td>SPSIPH</td>
<td>Pharmaceuticals Select Industry Index</td>
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<tr>
<td>TE</td>
<td>Therapeutic Equivalence</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>USPTO</td>
<td>United States Patent and Trademark Office</td>
</tr>
<tr>
<td>VA</td>
<td>U.S. Department of Veteran Affairs</td>
</tr>
<tr>
<td>VC</td>
<td>Venture Capital</td>
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<td>WTO</td>
<td>World Trade Organization</td>
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Chapter One

INTRODUCTION

Public Policy Background

Within the knowledge-based economy of the United States, technological industries, such as pharmaceuticals, life sciences, the energy sector and information technology, often rely on intellectual property (IP) protection as a primary driver for innovation. Intellectual property refers to inventions for which exclusivity rights are assigned to designated owners by law. Intellectual property rights (IPR) are the rights granted to the creators of IP and include trademarks, copyright, patents, industrial design rights, trade secrets and licensing agreements (Bessen, 2005; Halligan, 2010). Pharmaceuticals and biopharmaceuticals have an additional barrier to entry involving regulatory approval and governmental oversight of products.

As the U.S. transitioned from an industry-based to a knowledge-based economy, intellectual property, as an economic asset, is quantifiable and therefore should be included in calculations of economic output. When intellectual property is included in calculations of national gross domestic product (GDP) as intangible capital, a significant difference in the patterns of U.S. economic growth can be observed (Corrado, Hulten, & Sichel, 2006).

As IP protection rights became stronger and their scope broadened over the last three decades, the debate about the optimal level of such protections to drive innovation, balanced against the need for public access to the invention, became more contentious. Many theories and public policy arguments have emerged pertaining to whether or not IP protection and market exclusivity provide disproportionate benefits to monopolist IP holders to the detriment of society at large. The question debated is: how much monopoly protection is sufficient to stimulate
innovation and accelerate the progress in science and technology while balancing the dissemination of inventions with public access? (Mandel, 2012).

Policymakers and scholars debate the economically and socially optimal levels of legally enforceable rights for intellectual property, where pro-monopoly and pro-public access advocates argue the need for more IP protection (less public access) versus more public access (less IPR) to inventions.

The issue of balancing intellectual property rights against public access is particularly significant in the pharmaceutical industry, because IP protection policies may be an important mechanism for stimulating and rewarding innovation in this research-based sector (Kahn, 2007). Some argue that longer and stronger product monopoly protection may be necessary to stimulate the needed investment of capital for research and development (R&D) because it would give drug manufacturers a period of market exclusivity necessary to recapture their initial investment. Others argue that as intellectual property protections increase, incentives to innovate become greater, but consumers are subject to higher prices for a longer period of time (Posner, 2005). With decreased intellectual property protection, consumers’ costs are reduced, but there may be decreased incentives for manufacturers to invent new drugs, which results in fewer goods and services available to society.

At one end of the continuum of the greater public access–private property rights debate, some policy analysts argue that society is overall enhanced when exclusivity rights are minimal because the elimination of monopolistic pricing does not compromise the level of innovation. At the other end, commentators argue that stronger intellectual property rights are necessary to
stimulate innovation, and therefore society overall benefits from these increased technological and scientific advances.

Resolution of this debate requires identifying where along the continuum of protection versus access is the optimal balance for adequate invention incentives and public access. As Zinnbauer (2004) discusses, the desired position of the proper balance of IPR must be continuously reevaluated, because optimal levels of IP protection shift over time as technologies emerge and normative needs change.

Pro-access argument

Pro-access advocates propose that strong intellectual property protection is a deterrent to technological advances because it raises costs. Another consideration – as it pertains to pharmaceuticals – is that medications should be accessible to all patients at lower costs, and drug monopolies are an impediment to this societal need (Kesselheim, 2007). This construct theorizes that IP protection is an impediment to innovation because it prohibits the use of protected products for further research and development. Follow-on or enabling activities (i.e., the foundation for further inventions) are blocked by the exclusivity granted to the inventor.

Additionally, the pro-access theory assumes that creativity is not driven by monetary rewards because inventors of new products develop new ideas for personal intellectual satisfaction (Granstrand, 2006). However, this assumption that innovation is driven mostly by the creative spirit is not applicable to many modern technology sectors, such as pharmaceuticals. Pharmaceutical research requires exceedingly large capital investments and therefore is not feasible for realization by creative individuals without financial resources mostly available to for-profit corporations (Kesselheim, 2007).
Pro-monopoly argument

Pro-monopoly advocates argue that stronger intellectual property protection is essential for innovation (Fisher, 1999). The underlying assumption of this argument is that intellectual property protection – by means of creation of private property rights – is instrumental in motivating inventors (and companies) and therefore stimulates innovation (Corrado et al., 2006). Innovation is greater in industries where innovators rely more on IP protection. These theories defending stronger monopoly protections are based on free-market analysis of productivity and economic growth (Posner, 2005).

Researchers that advocate for a pro-monopoly regime tend to treat intellectual property as an intangible asset that has monetary value and therefore adds to a company’s balance sheet, thus increasing the enterprise’s value. These theories apply more directly to research and development-intensive sectors of the economy (e.g., pharmaceuticals, life sciences) because innovation in these sectors requires substantial capital and resources. Hence, governments must create enabling environments that encourage innovation and the corresponding investment in intellectual property (Horii & Iwaisako, 2006).

There is a positive relationship between IP protection and product market competition using growth models with step-by-step innovation (Aghion, Howitt, & Prantl, 2014). Longer exclusivity prolongs the period over which the firm escapes competition and receives higher monopoly rents from its technological advances. A firm may have an increased incentive to innovate when there is a gap between the post-innovation pricing (i.e., marker exclusivity) and the pre-innovation rent (Qian, 2007).
Supporters of stronger IP protection propose that in knowledge-based economies, intellectual property protection plays a fundamental role in the decisions to invest in innovation (Atun, Harvey, & Wild, 2006). They posit that since research-intensive sectors, such as life sciences, are critical to the well-being of society, IP protection is therefore necessary to achieve greater public good through stimulation of capital investment into research and development, with the tangible benefit to society of more advanced technology and the resulting useful products (e.g., pharmaceuticals targeted for debilitating diseases).

Reconciling the pro-access and pro-monopoly arguments

While a number of authors articulate the view that strong intellectual property protections provide an overall benefit for the economy and, consequently, for society (Posner, 2005), a large number of scholars and researchers have differing opinions on IP protection ranging from proposals to virtually abolish exclusivity rights (Kesselheim, 2007) to suggestions to use them selectively based on numerous factors (e.g., capital investment, barriers to entry and medical importance of a drug). Others propose theories that alternative incentive schemes must be developed to encourage innovation (Gallini & Scotchmer, 2001). These divergent perspectives should be considered by policymakers when designing an optimal level of protection for pharmaceutical inventions.

There are commentators who try to reconcile both needs and propose a modified approach to intellectual property protection. For example, Mandel (2012) argues that social welfare considerations are of greater importance than what the quantitative law-and-economics analysis ascribes to the societal access variable. He proposes that the patent term and scope must reflect the need of society to have greater access to the invention because the ultimate goal of
innovation is to improve the overall well-being of humanity. Mandel suggests that the delegation of monopoly-granting authority should be transferred to an independent institution that would determine the length and scope of market exclusivity on a case-by-case basis using the analysis of sunk costs (i.e., cost of development) of the invention measured against the societal need for access.

Another example of the theoretical framework that moves closer to free-market economics, where society benefits from competition within the marketplace, brings forward the idea that while market exclusivity increases the reward for innovation, very strong IP rights ultimately reduce the number of competitors (Horii & Iwaisako, 2006). This theory of the optimal level of IPR protection depends on the technological complexity of the invention and structural impediments (e.g., significant capital or highly skilled labor) to innovate. Additionally, the level of IP protection must consider the desirability of the invention measured in terms of the societal need for the invention (Horii & Iwaisako, 2006).

**Intellectual Property Protection and the Pharmaceutical Industry**

The pharmaceutical industry is critically important to society because it brings innovative therapies to patients helping them live longer healthier lives. Regardless of each person’s individual health status, the vast majority of people rely on pharmaceuticals at some point in their life. As an ancillary application, new biotechnology products often arise from research undertaken by pharmaceutical companies, and the progress of life sciences is closely related to the pharmaceutical industry (Drahos, 2009).

The pharmaceutical industry is also very important to the U.S. economy. In 2016, the U.S. pharmaceutical sector accounted for more than 45% of the global pharmaceutical market;
together with Canada and Mexico, it represents the largest continental pharma market in the world (Statista, 2017). Many of the leading global pharma companies are from the United States with 6 out of top 10 revenue companies in 2016 being from the U.S. (Statista, 2017).

Due to the high costs of drug development and testing, as well as the lengthy approval process by the Food and Drug Administration (FDA), the pharmaceutical industry, more than other sectors, relies heavily on the ability to have market exclusivity for their newly-developed products (Terry & Lesser, 2015). After the safety and efficacy of a drug have been established, the direct cost of manufacturing is relatively low (Scherer, 2007). The low manufacturing cost is the reason why generic drugs can be mass produced and sold at a price that is significantly lower than that of the pioneer brand-name drug. However, it is the original developer who bears the initial costs of research, testing and approval of the drug before it can be marketed to patients. Additionally, as part of the nature of life science research, not all new projects yield effective products, resulting in significant sunk costs to the companies (Worthy & Kozak, 2010).

Because of these considerations, pharmaceutical companies must conduct a cost-benefit analysis and assess their potential to recapture the original investment and reap financial profits before embarking on pre-clinical and clinical trials for a potential new therapeutic. The development of pharmaceutical products often relies on a substantial amount of initial investment and knowledge, but it can be relatively easy and inexpensive for competitors to reproduce the product once it is introduced into the market (European Commission, 2008).
Historical Overview of Past Policy Reforms to Strengthen Pharmaceutical IP

1980
Bayh-Dole Act affirmed the right of universities to patent and license the results of government-sponsored research.

1983
Orphan Drug Act (ODA) was passed to facilitate development of drugs for rare diseases (i.e., orphan drugs) affecting less than 200,000 Americans. Companies that developed drugs meeting this requirement received several incentives including seven-year market exclusivity.

1984
Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) Amendments, 35 U.S.C. § 156 allowed extension of the patent term to compensate for delay in marketing authority for the FDA to sell new drugs. This represents a compromise after the Federal Circuit’s decision in *Roche v. Bolar*, 221 U.S.P.Q. 937 (Fed. Cir. 1984) that held that premarket testing (required by the FDA) by a generic drug manufacturer constituted patent infringement.

1986
United States succeeds in having international intellectual property rights protection placed on the negotiating agenda for the Uruguay Round of negotiations of the General Agreement on Tariffs and Trade (GATT).

1994
Uruguay Round of negotiations for revision of GATT concludes an agreement on TRIPS, which includes enforceable minimum standards for patent protection. TRIPS is the acronym for the agreement on Trade-Related Aspects of Intellectual Property Rights administered by the World Trade Organization (WTO), which outlines the minimum standards of many forms of intellectual property regulations for WTO members.

1995
Implementation of the WTO’s Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreement) and changing the patterns term in the U.S. from 17 years since the patent issue to 20 years from the filing date.

1995
Biotechnology Process Patent Act Protection amended 35 U.S.C. § 103(b) for biotechnology processes from finding of obviousness if it is for the production of a new and nonobvious product.
The IP regime is regulated at the federal level, while state and local governments lack jurisdiction to shape national IP policy (Varian, 2005). Intellectual property policy changes discussed below were important reforms because their major goal was to affect the level of innovation within sectors of the economy that rely on IP for their growth. The Bayh-Dole Act (1980) and Hatch-Waxman Act (1984) shifted patent policies to stimulate the creation and growth of life science companies (Mehl, 2006).

*Bayh-Dole Act, 1980*

The Bayh-Dole Act of 1980 transformed the parameters for academia and private industry collaboration (Atun *et al.*, 2006). The Act allowed universities to own the intellectual property they created, and therefore more freedom became available to educational institutions to enter into licensing agreements with the private sector, venture capitalists or foreign firms. This enabled the universities to receive substantial rewards for undertaking successful academic translational research. As of 2006, the Act resulted in approximately 42,000 licensing deals completed by U.S. universities and created over 4,500 companies producing countless products and services (Atun *et al.*, 2006).

*Orphan Drug Act, 1983*

The Orphan Drug Act (ODA) of 1983 was passed by Congress to encourage the development of drugs for rare diseases (e.g., Huntington's disease, amyotrophic lateral sclerosis and muscular dystrophy), which affect less than 200,000 individuals within the United
States. Prior to enactment of the Act in 1983, only 38 orphan drugs had been approved. By 2014, this number increased to 373 approved drugs targeting 468 indications (Hadjivasiliou, 2014). The rationale for the legislation was that the market for any drug with such a limited application scope would be unprofitable due to the small number of potential patients. Therefore, it was argued by stakeholders that legislative action was necessary to encourage pharmaceutical manufacturers to develop orphan drugs (Cheung, Cohen, & Illingworth, 2004). The grant of market exclusivity is considered to be among the greatest incentives for manufacturers because, unlike patents, the period of exclusivity does not begin until the drug receives FDA approval, and it is independent of the drug’s patent status (Carson, 2000).

This market exclusivity is similar to the provision in the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which grants 12-year market exclusivity. In his 2009 statement to the House Subcommittee on Technology and Innovation of the Committee on Science and Technology, Dr. Anthony Mire-Sluis, Amgen’s Executive Director of Global Product Quality and Quality Compliance, pointed out the success of Orphan Drug Act as an example of exclusivity positively affecting innovation. “Strong protection of intellectual property—both patents and data—is the cornerstone of any research-intensive, innovation-driven industry. Failure to ensure adequate intellectual property protection will undermine investment in biotech innovation. Without it, venture capital that is the lifeblood of startup companies will divert resources to investments with more certain returns, regardless of their social value. Investment decisions by more mature biotech companies that are self-funding are necessarily driven by the possibility of recovering the cost of bringing a product to market because this funds the next discovery. Without adequate intellectual property protection, research and development will be greatly diminished. This is a very expensive proposition for patients waiting for cures. We know
that incentives to invest can be successful. For example, Congress has put in place incentives to encourage orphan drug development” (House Hearing 111-53, 2009).

**Hatch-Waxman Act, 1984**

In the early 1980s, there was a concern that very few generic drugs were entering the market because innovator pharmaceutical companies were able to make it difficult for generic manufacturers to successfully file Abbreviated New Drug Applications (ANDAs). In 1983, only 35% of top brand-name drugs with expired patents had a generic version (Boehm, Yao, Han, & Zheng, 2013). Drug Price Competition and Patent Term Restoration Act (commonly referred to as the Hatch-Waxman Act) was enacted to encourage generic small-molecule drug manufactures by establishing an abbreviated path to the approval of generics.

While the Act facilitated generic manufacturers filing ANDAs for their follow-on drugs (i.e. generics), it also provided protections for innovator companies via two mechanisms. One of them was a new 5-year data exclusivity period established for new chemical entities (NCE) whereby the FDA cannot approve a generic for 5 years following the approval of the novel drug. The other mechanism of protection was the ability of innovator companies to extend the term of their patents by a portion of the time that it took the FDA to approve the drug (Mehl, 2006).

For generic drug manufacturers, Hatch-Waxman Act simplified the process of filing ANDAs by explicitly prohibiting the FDA from requiring any information other than manufacturing process, quality assurance and bioequivalence (i.e., a study that demonstrates that the generic drug follows the same biochemical mechanism within the body as the innovator
Additionally, the Act provided generic companies with the research exemption, which is essentially a safe harbor from patent infringement litigation during the period of ANDA preparation when the company is learning how to manufacture the generic, produces a test batch and conducts studies on bioequivalence (Mehl, 2006).

The Hatch-Waxman Act of 1984 started a new chapter in the pharmaceutical industry which now experienced a boom in the approval and production of generic drugs. Before the Act, in 1983 only 13% of prescriptions were filled with generic drugs; however, by 2012, this number increased to 84% (Boehm et al., 2013).

**Patent Term Extension and Restoration, 1984**

Pharmaceuticals have a long lead time between submission of an application to the FDA (subsequent to or concurrent with the filing of a patent application in the USPTO) and when the FDA grants approval to the company to begin marketing the product to patients. This results in a long delay between the time of the original invention and ability to sell it to the public. While this is a necessary process to ensure safety and efficacy of the new drug to minimize potential harms that may be caused to consumers, this extended delay reduces the effective patent term of exclusivity (Lerner, 2002). In 1994, Congress permitted the patent term to be extended for pharmaceutical companies under Section 156 of the Hatch-Waxman Amendments. This policy reform was made to compensate for delay in marketing authority (i.e., when the drug becomes available for sale) from the FDA to sell new drugs to patients (Sampat & Williams, 2015).
Since the development of pharmaceuticals is a capital-intensive activity, the additional time for the patent term may be important to the company when they project the net profits from developing the drug. Therefore, this reform was perceived by the pharmaceutical industry as beneficial for encouraging innovation in pharmaceuticals by making the effective period of market exclusivity more comparable to that of patented products in other industries that do not have the associated delay of regulatory approval.

TRIPS: Patent Term Extension of 1995

In 1994, the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) was negotiated during the Uruguay Round with 123 countries participating (Falvey, Foster, & Greenaway, 2004). The Uruguay Round led to the creation of the World Trade Organization (WTO) and the General Agreement on Tariffs and Trade (GATT) (Khoury & Peng, 2011). From the negotiations, GATT trade rules extended to protecting intellectual property.

The Uruguay Round came into effect in 1995 with additional deadlines in 2000, while developing nations had until 2004 to adopt specific provisions of intellectual property protection (Cockburn, 2011). In 1995, the United States changed the term of patent exclusivity from 17 to 20 years to make the U.S. patent term conform to TRIPS.

In addition to the patent term extension, commencement of the patent term was set to the priority date (i.e., filing date of the patent) and not the issue date of the patent. Under the prior patent system which used the issue date, the invention disclosed in the patent application was not published until the patent was issued, which is often several years after filing (Kyle & McGahan,
2008). This delay in publication of the invention was more pronounced in pharmaceutical patents due to the time needed for the patent examiner to process the patent application and compare the new invention’s written description that accompanies the application to prior art, which includes both patented and non-patented known inventions (Williams, 2015).

New Category of Drugs – Biopharmaceuticals (Biologics)

What are biologics?

In general, the active substance in a product regulated as a drug can usually be defined at the molecular level (Simmons, 2010). Historically, drugs have been defined as small-molecule compounds produced by laboratory methods of organic chemistry (Brougher, 2010). Recent advances in biotechnology, monoclonal antibody technology and the deoxyribonucleic acid (DNA) nucleotide sequences elucidated from the Human Genome Project have facilitated the development of new target medicines, referred to as biologics (Boehm, 2007). Biologics are not classified chemically the same as small-molecule drugs because they are much larger and more complex molecules than the conventional, more common small-molecule therapeutics traditionally sold by pharmaceutical companies (Harbour, 2009).

Biologics are typically protein-based medicines created through the generative functions of living organisms, such as bacteria, yeast and mammalian cells (Leader, 2008; Seamon, 2010). They include therapeutic proteins, vaccines, monoclonal antibodies, allergenics and gene therapies as some of the most clinically and financially significant pharmaceutical products in
the U.S. (Silber, 2013). Many biologics are more complex and often are mixtures of biopharmaceutical components (Simmons, 2010).

Biologics are very large and structurally complex molecules often produced from living organisms (e.g., bacteria or cell culture) requiring extensive isolation and purification steps, unlike traditional small-molecule drugs created through chemical synthesis (Corbitt, 2008). They are characteristic of recombinant drugs and their properties are highly dependent on the production process. Process variables include concentrations, the temperature of production, molecular weight and the amino acid sequence of the produced protein (Leader, 2008).

Biologics have some of the highest efficacy rates for treating patients with many common disorders and diseases (e.g., cancer, diabetes), but remain one of the most expensive categories of drugs. Production of biologics requires more difficult and expensive processes and techniques (Silber, 2013). Due to the large size and complexity of biologics, their average cost to develop and manufacture is more than 20 times that of a small-molecule drug (Gehani, 2011). The Federal Trade Commission (FTC) reports that one year of treatment with a biologic can often cost between $50,000 and $250,000 (Silber, 2013; Overley, 2014).

Economics and Market Significance of Biologics

Biologics are gaining popularity within the pharmaceutical industry and becoming a larger proportion of the total amount of new biopharmaceuticals. In 2015, the biopharmaceutical industry was expected to be valued at almost $793 billion worldwide (Carlson, 2010). In 2008, about 30% percent of the top one hundred pharmaceuticals were biologics, while in 2009 they
constituted about one-third of the top fifteen pharmaceuticals (Brougher, 2010; Pugatch, Torstensson, & Chu, 2012). In 2014, U.S. biopharmaceutical industry supported nearly 854,000 direct jobs, 3.5 million indirect and induced jobs, and generated more than $1.2 trillion in U.S. economic output (Helwig, 2016).

More than 50% of the U.S. prescription drug budget is expected to be spent on biologics by 2018. By 2020, the global market for biologics is forecasted to exceed $390 billion, with significant cost-saving attributed to biosimilars (Aitkens, 2016). Over 20 biologics in the U.S. with a market value of over $50 billion will lose monopoly protection secured by patents by 2019 (Malkiewicz, 2016).

Approximately 40% of all pharmaceutical R&D and products in the pipeline involve biopharmaceuticals rather than traditional small-molecule drugs (Malkiewicz, 2016). One concern is the need for regulation to prevent unethical copycats from extracting unfair advantages from the public and damaging the goodwill of reputable manufacturers of pharmaceuticals (Choi & Thum, 1998).

Challenges for the creation of follow-on biologics

Generic drugs (regulated under the Hatch-Waxman Act) are chemical copies of the innovator drug. While it is possible to make an exact copy of a small-molecule compound (i.e., pharmaceutical), biologics are much larger (e.g., tens of thousands of atoms long compared to just a few thousand atoms for small-molecule drugs), and therefore it is exceedingly difficult to
exactly duplicate the biologic molecule and create a generic product that is identical to the innovator biologic (Mounho, 2010).

Additionally, biopharmaceuticals are difficult to replicate because of the complexity of the production process, such as temperature and concentrations (Pipes, 2008). Most biologics must be grown in living organisms and often involve modified DNA, and even with the same chemical formula and process, each molecule of a biologic may have a slightly different structural pattern (Roger & Mikhail, 2007).

A biosimilar, unlike a small-molecule generic drug, is a product that is similar to, but not the same as, the innovator (reference) biologic. Therefore, the FDA determined that the approval pathway used for generic small-molecule drugs would not be sufficient for complex biologics (Frank, 2007). Even a small difference in a biopharmaceutical molecule can cause uncertain outcomes and lead to health hazards such as effectiveness, safety or ability to produce an immune response (Troy, 2007). A minor change in the manufacturing process can result in adverse effects in a patient’s immune response (i.e., immunogenicity) (Sharma, 2007). Therefore, a change from one biologic medicine to another biosimilar can have serious health consequences (Shedden, 2008).
Chapter Two

BIOLOGICS PRICE COMPETITION AND INNOVATION ACT (BPCIA)

Legislative History

The FDA drug approval process is slow, legally complex and scientifically challenging. For traditional pharmaceuticals, acceleration of the FDA approval process and automatic substitution provisions are credited with robust brand-to-generic competition in the traditional pharmaceutical marketplace. This competition is, to some degree, responsible for substantially reducing drug prices and total prescription expenditures in the U.S. (Silber, 2013). The regulatory approval process for therapeutics differs by the classification of the compound. Pioneer small-molecule drugs are regulated by the Federal Food, Drug, and Cosmetic Act of 1938 (FDCA), generic small-molecule drugs by the Hatch-Waxman Act (Davis, 2013).

Because biologics are not regulated under the Hatch-Waxman Act, they are not subject to the Act’s accelerated FDA approval. They are also not covered by the state laws that allow pharmacists to automatically substitute a generic for a brand-name drug (Simmons, 2010). Over the last decade, Congress and policy analysts have recognized the lack of a similar abbreviated approval pathway for biologic products as an impediment to stimulating the introduction of less expensive therapeutics (Haas, 2005; Schacht, 2008).

A new regulatory pathway for biologics and biosimilars was necessary because the Hatch-Waxman amendments regulated products under the FDCA and (except for one provision on patent term restoration) not to those products regulated under the Public Health Service (PHS) Act. While the European Union (EU) approved such a pathway in 2004, the U.S. was not among the countries that had a pathway for biosimilars (Simmons, 2010).
On March 23, 2010, President Obama signed into law the Biologics Price Competition and Innovation Act of 2009 (BPCIA), which created a statutory pathway for approval of biological products, as well as a scheme for litigation of their associated patents. Prior to this, a number of events and developments occurred over several decades, leading to the general understanding by stakeholders that there was a need for a distinct and abbreviated pathway for approval within this emerging field of biotechnology. Stakeholders included the Food and Drug Administration, the Federal Trade Commission (FTC), Democrats and Republicans in both the House and Senate, patient advocacy groups, trade associations and professional organizations, such as the Drug Information Association (DIA), among others.

Prior to the enactment of the BPCIA in 2010, there was an overlap between small-molecule drug statutes and the biologics statutes, which played a significant role in the review and approval of biosimilars. The Patent Restoration Act of 1984 (i.e., Hatch-Waxman amendments) created legislation that became a model for how to best shape the future approval of biosimilars under the FDCA (Price & Rai, 2016).

The FDCA was passed by Congress in 1938, giving authority to the U.S. Food and Drug Administration to oversee the safety of food, drug and cosmetic products. In 1944, Congress amended the Public Health Service Act (PHSA) by adding the Biologics Act as Section 351, which specified that a license to manufacture would be issued to manufacturers who demonstrated the “safety, purity and potency” of the biological products (Beers & Karst, 2017). This new language was interpreted as requiring both an approved Establishment License Application (ELA) and an approved Product License Application (PLA). The dual licensure requirement lasted until 1997 when Congress eliminated it and created a single biologics license
application (BLA). The result of this legislation paralleled the FDCA statute regulating new drugs (Drabant, 2011).

The federal regulations of biologic and non-biologic products had been separate, yet overlapping with one another (Timmis, 2015). Three primary considerations have facilitated the development of the BPCIA. First, the governing statutes were enacted separately and administered by separate agencies. Second, the precise elements of the law regulating biologics were unclear and some protein products (i.e., biologics) were approved under the FDCA. Third, all biologics are also drugs, therefore are subject to the FDCA and, theoretically, are required to have a New Drug Application (NDA). This lack of symmetry and obvious contradictions led, in some measure, to the development of the BPCIA (Drabant, 2011).

Addressing Overlap between FDCA and PHSA

There were four major attempts to harmonize the rules governing biologic and non-biologic drugs. In 1995, the FDA proposed to eliminate the dual licensure – ELA and PLA requirements – for well-characterized therapeutic biotechnology-derived drugs. First, in 1997, Congress added Section 351(j) to the FDCA, which codified the agency practice of not requiring NDAs for licensed biologics with approved BLAs (Carver, Elikan, & Lietzan, 2010). The FDA’s effort was replaced by the enactment of the Food and Drug Administration Modernization Act of 1997 (FDAMA), which eliminated the dual licensure requirement for all biologics by substituting the BLA requirement. Second, Congress reaffirmed that the FDCA applies to biological products. Third, the FDAMA directed the Secretary of Health and Human Services (HHS) to minimize differences in the approval of license applications under Section
351 of the PHSA and products approved under Section 505(b)(1) of the FDCA. Fourth, the FDA unified the BLA and NDA review processes. For example, in 2003, the FDA consolidated the review for most therapeutic proteins – both NDAs and BLAs – to just its drug center, as opposed to both the drug center and biologics center (Kingham, Klasa, & Carver, 2014).

The Influence of Biosimilars in Europe on the United States

The EU established a unified system for the approval of both drugs and biologics before the United States. A biologics pathway was developed in Europe between 2003 and 2004, with the first approval of a biosimilar in 2006 (Schiestl, Zabransky, & Sorgel, 2016). At a 2004 hearing by the U.S. Senate Committee on the Judiciary, Senator Schumer addressed his colleagues by stating: “Companies are already marketing safe, effective and affordable biologics in Eastern Europe, Russia, Asia and Latin America. They are not yet available in the EU, which has a system of drug regulation similar to ours. But the EU has issued guidance on how biologics could be done. They issued that several years ago and they are well on their way to approving several follow-on biologic products [biosimilars]. So, unfortunately, in this area America lags sadly behind many other countries. Surely, if the science is adequate to produce these products elsewhere, especially in Europe where the system of regulation, as I mentioned, is similar to ours, we can do it here. So we have got to get the process rolling” (Senate Hearing 108-635, 2004).

The pressure was mounting on Congress to start acting on the matter and bring forth a sensible legislation for the approval pathway for biosimilars that would address the issue of high costs to patients and spur biologics innovation. Multiple hearings were held by various Senate
and House committees where industry leaders were invited to testify and give their perspective on several issues associated with legislation of this nature, such as similarity, interchangeability, exclusivity, patent litigation and more.

When testifying during the 2006 hearing of the Senate Special Committee on Aging, Mark Merritt, President and CEO of the Pharmaceutical Care Management Association (PCMA), along with others urged lawmakers to act. “PCMA believes Congress should establish a clear legal pathway to approve biogenerics [biosimilars] sooner rather than later. Last year alone, the cost of biologics soared 17.5 percent, compared with traditional drugs which increased by 10 percent, and biologic costs are expected to represent $90 billion of drug spend in 2009. Obviously, there are no generic alternatives to make prices more competitive in this area. Traditional [small-molecule] drugs are created from chemicals, whereas biologics are derived from living organisms and are regulated differently by the Federal Government. While some argue that the science of creating generic biologics is not fully developed, progress is being made on a daily basis and the European Union has already approved legislation that creates a regulatory pathway for the approval of biogenerics [biosimilars]. For these reasons, PCMA recommends that Congress create a clear legal pathway for generic biologics which would allow for some needed competition to bring down prices” (Senate Hearing 109-685, 2006).

This concern of cost savings for biologic drugs was echoed by Senator Hillary Clinton. “A lot of scientific advances have been made and the biotechnology industry is now an integral part of our pharmaceutical industry. I think we have to update the law to reflect the critical role that biologics are now playing in treatment of disease. Biologics are a major driver of increasing prescription drug costs. Six biotech pharmaceuticals are generating more than $1 billion in sales
and the top three biotech pharmaceuticals — Neupogen, Epogen and Intron-A — cost patients $23,000, $10,000 and $5,000, respectively, each year” (Senate Hearing 109-685, 2006).

Later in 2006, the President and CEO of Consumers Union, Jim Guest, urged the Senate Committee on Health, Education, Labor, and Pensions to follow the EU’s lead: “There is no clear law providing for the development of generic versions of more complex molecular biologic medicines. These new products are the most expensive medicines on the market--some costing as much as $100,000 to $250,000 for a course of treatment. Some criticize the notion that biogenerics could bring cost-saving benefits, saying that these drugs are far more complex than other drugs because they are made from living organisms, and therefore cannot be copied as easily, as inexpensively, or as safely as other drugs. Nevertheless, the European Medicines Agency is creating a framework for biogenerics to be approved. Consumers Union joins most other observers in believing that biogenerics could provide some savings and can be provided safely, thus helping some of our most severely ill patients. The law should be clarified to allow us to do what the Europeans are doing: bringing some relief to consumers” (Senate Hearing 109-850, 2006).

In March of 2007, the U.S. Senate Committee on Health, Education, Labor, and Pensions convened again to hear more testimony on follow-on biologics. Among the invitees was Dr. Nicolas Rossignol, a Senior Administrator of the European Commission Pharmaceuticals Unit. When questioned by Sen. Enzi as to the involvement of industry during the process of crafting biosimilars legislation in Europe, Dr. Rossignol’s response was: “Involving the industry, but also other interested parties such as patients associations or healthcare professionals, enabled us to gather as much expertise in the field as possible (which, depending on the type of product concerned, may be limited). This allowed regulators and
scientific experts at the EMEA/European Commission to confront their vision with the practical experience of manufacturers, doctors, etc. It also helped us to better understand which therapeutic areas and product classes are likely to emerge first in the field of biosimilars (e.g., insulins, growth hormones...). Last but not least, involving both sides of the industry enabled a constructive exchange of contradictory views and facilitated the development of a balanced, unbiased regulatory framework. Transparent involvement of both the generics/biosimilar and the innovative industry, together with strong assurance of the independency of the scientific experts involved in the establishment and implementation of the regulatory framework, are in my opinion key factors to ensure that legitimate scientific issues are considered but dilatory tactics do not derail the process” (Senate Hearing 110-375, 2007).

However, Senator Schumer had words of caution for his colleagues about blindly following the EU. “I want to welcome Mr. Rossignol from the EU to this hearing because the EU has already moved forward on approving what they refer to as biosimilars and I think their experience is valuable but I would urge the committee to consider this experience carefully. There may be valuable lessons to be learned from a system that is already in place but we must fully understand how that model might work in our own market. First, we should understand how the EU system came to be and how it worked in practice. As it stands today, the EU has a highly regulated process in place that has arguably, at least and unnecessarily burdensome to competitors and here’s the interesting fact. It has only resulted in two approvals to date [2007]. This process was not established by legislation that was passed by the European equivalent of Congress, however. The statute that created a pathway to biosimilars in the EU was written in broad language, which gave Europe’s equivalent of the FDA discretion to flesh out the details. So when I think about the EU model, I agree we should pass legislation that would give the FDA
the discretion but why would the United States want to deprive the FDA of the ability to draft its own regulations and force them to swallow a complex set of regulations that has been created by another government, a system of government that has a different way than ours. It has price controls and the EU’s generic market is not as robust as the market that Senator Hatch and Congressman Waxman created” (Senate Hearing 110-375, 2007).

A similar position on following the European prototype for biosimilars legislation was expressed by Novartis’ VP and Global Head of Biopharmaceutical Development Dr. Ajaz Hussain. “In general, the EU approaches on follow-on biologics per se, their so-called “biosimilars,” suit an EU environment of 27 distinct countries with different legislative and regulatory histories as well as very different health care and reimbursement systems. The United States needs a solution that suits U.S. needs and statutory environment as it has been evolving here for over 200 years following adoption of the U.S. Constitution” (Senate Hearing 110-375, 2007).

In the summer of 2007, lawmakers in the U.S. engaged in key negotiations over biosimilars legislation. Shortly thereafter, eleven biosimilars had been approved in Europe. Both the House and the Senate were advancing various versions of a biosimilars legislation, though none were getting closer to becoming a law. At a 2009 hearing of the House Subcommittee on Health of the Committee on Energy and Commerce, a senior health policy analyst for the Consumers Union, William Vaughan, invoked European regulation again when he stressed the urgency of the matter by saying: “As of last June, Europe had approved over 10 of these [biosimilars], and I am assuming they have gone higher, and we are sitting here paralyzed. And so we hope you can come together and work something out because that is essential” (House
Hearing 111-54, 2009). However, early reports of market penetration for biosimilars in Europe indicated a lessening of the potential cost savings for biosimilars (Johnson, 2016).

**Recent Developments in the U.S. Patent Law Leading up to the BPCIA**

Spanning last two decades, several developments in U.S. patent law affected the patent rights for biologic inventions and informed the discussions of the patent litigation provisions of the biosimilar legislation. One important patent development involved the limitation of the doctrine of equivalents, a judicially-created doctrine to prevent third parties from avoiding a finding of patent infringement by departing insignificantly from the literal scope of the patent claims. *Warner-Jenkinson* (1997), while reaffirming the doctrine, substantially limited it by estopping the patent holder from reclaiming scope that was “negotiated away” by amendments to claims during patent prosecution to obtain issuance; this was in part to provide fair notice to potential infringers.

Another important patent law element is the statutory requirement for a written description of the claimed invention, which “must be sufficient to enable a person of ordinary skill to make and use the invention.” The inventor needed to “fully characterize” the biotechnology compound (e.g., structure, formula, physical properties) and deposit the compound in the public depository decided in *Ariad* (2010). Concurrently, the United States Patent and Trademark Office (USPTO) issued guidelines that patent claims directed to a genus of proteins required that a representative number of species be fully described in the written description of the patent application. Therefore, inventors of biologics are less likely to obtain (or
be able to successfully enforce) broader claims directed at the entire genus of proteins or nucleic acids (Carver et al., 2010).

Arguably, the most important development affecting patent rights was the eBay Inc, 2006 decision that changed what patent owners relied on as a presumption of an injunction following a finding of infringement to the traditional four-factor test requiring irreparable injury, such as injury to competitive reputation, rather than money royalties. In part, eBay was directed, as stated in the concurring opinions, against “non-practicing entities” (patent trolls) that did not commercialize the patent except by licensing after suing. The unavailability of an injunction to such entities (including universities) took away that important leverage, severely devaluing patents for non-practicing groups. The Hatch-Waxman amendments provided an automatic permanent injunction, but the eBay decision meant that there would be no similar provision in the biosimilar legislation (eBay Inc, 2006).

The relative importance of patents protection and data exclusivity could be significantly different between biologics and traditional small-molecule drugs (Carver et al., 2010). During the 2009 hearing in front of the House subcommittee on Courts and Competition Policy of the Committee on the Judiciary, Attorney Jeffrey Kushan was among the witnesses speaking on behalf of the Biotechnology Industry Organization (BIO). Attorney Kushan offered a valuable analysis of how patent protection for biologics differs from small-molecule drugs. “Some have suggested that data exclusivity provided today for small-molecule drugs will be adequate for biological production. Several factors explain why this is not true. Studies have shown that in the small-molecule area, on average, generic competition starts around 12 to 14 years after the innovator product is launched. Patents are why that happens. Patents can do that because any generic drug must be structurally identical to the innovator product. That means [small-
molecule] drug innovators do not need broad patent claims to protect their investments. They can protect their innovative drug products with what we call picture claims on the exact molecule. All this means is that a small-molecule drug innovator deciding whether to make the investment and start the 10 to 15 year path to develop and bring a new drug to market today can assume that their patents, if they are upheld, will prevent the marketing of an infringing generic product until those patents expire. This is not going to be true for biological products. Biosimilar products will invariably have different structures than innovator products. The biosimilar bills we see today all do not require structural identity. Compounding this problem is the problem that most biotech patents issuing today are narrow. Let me say very clear, these are not weak patents. They are very strong and effective patents. They are just narrow patents. The same uncertain science that makes it difficult to make an exact copy of a biological product is actually why we have narrow patent rights. Together, these two factors [simplicity of small-molecule drugs and narrow patent claims] make it impossible for an innovator to predict when it is deciding to invest in development of the product whether its patent estate is going to provide effective protection against a future biosimilar product, and that is why the Hatch-Waxman model as it exists today cannot be directly applied to the biosimilar environment. This patent loophole must be closed by the data exclusivity provisions” (House Hearing 111-73, 2009).

Biosimilars between 1998 and 2006

The years between 1998 and 2006 provided the backdrop for the enactment of the BPCIA legislation of 2010. Commentators reported an increasing pressure on the FDA and Congress during this period, which ultimately gave rise to the proposed legislation in 2009 and enactment
in March 2010. Historically, this was not a rapid process and resulted in several false starts from the FDA and several reworks within the legislature. Importantly, the biotechnology revolution and production of recombinant proteins approved under the FDCA accelerated the discussion of enacting a biosimilar legislation. In May 2006, the first biosimilar Omnitrope (the first recombinant copy of a biotech drug) was approved under the FDCA, which signaled that legislation was on the horizon (Kayser & Warzecha, 2012).

In June 2004, one of the earliest legislative committee hearings on biologics and biosimilars (though the term “biosimilar” was not yet in active use) since the enactment of the European law was held by the Senate Committee on the Judiciary. At that time, the issue of intellectual property protection for innovative biologics was discussed actively. Senator Orrin Hatch was the Chair of the Committee and brought up this issue in his address. “As a coauthor of the Drug Price Competition and Patent Term Restoration Act of 1984, I firmly believe that whatever we do on the legislative front should observe a principle of attempting to balance incentives for both pioneer and generic drug firms. While I am all for rolling up our sleeves to work to help develop an abbreviated approval system for off-patent biologics, we must be properly respectful of the intellectual property of the research-based firms because this is what undergirds the whole pharmaceutical enterprise” (Senate Hearing 108-635, 2004).

Among the key witnesses at the hearing was Lester Crawford, FDA’s Acting Commissioner who drew attention to the importance of economic incentives for innovation. “Medical innovation is a complex process, but one that can bring great value to patients. To realize the full benefits of medical innovation, it is important to adopt policies that protect incentives to develop new drugs and medical devices. Achieving this goal requires a delicate effort to strike a proper balance. Promoting innovation requires the right mix of incentives,
safeguards and effective regulation to secure maximum benefit from safe and effective new medical technologies, while assuming mechanisms for broad and equitable access to these new treatments” (Senate Hearing 108-635, 2004).

Representing one of the major biotech players, Amgen, was David Beier, Senior VP for Global Government Affairs, who outlined the state of the affairs at that time. “In 2004, there are 1,100 biotech companies. Only a handful of them make money. There are only 155 products on the market and there is no regulatory pathway, no scientific basis for the approval of follow-on products until and unless a process like the one Commissioner Crawford outlined takes place. … Current law does not provide the FDA with authority to approve follow-on biologics. We welcome the invitation from this Committee to begin a dialogue about a regulatory pathway for follow-on biologics. We believe that Congress must protect innovation before the FDA proceeds with the first steps toward a rulemaking or even a public process leading to guidance on science issues” (Senate Hearing 108-635, 2004).

In September 2006, Representative Waxman introduced the first biosimilars bill in the House, H.R. 6257, while Senator Shuman introduced almost identical legislation in the Senate. In April 2007, acting FDA Deputy Commissioner for Operations commented on differences between evaluating a new biosimilar and evaluating changes to a licensed biologic (Woodcock, 2007).

Emergence and enactment of BPCIA

Interest in legislation for a biosimilar bill increased through the end of 2006. Three bills were introduced between February and May of 2007, and hearings were held in both the House
and Senate between March and May. Some of the primary issues debated were comparability guidance, clinical data requirements, comparable products despite differences in amino acids or post-translation modifications, interchangeability between a biosimilar and reference product, intellectual property protections and data exclusivity (Carver et al., 2010).

Provisions of the proposed biosimilars legislation were debated, and amendments added during the next two years until the House voted and passed H.R. 3962 on November 7, 2009, and the Senate voted and passed H.R. 3590 on December 24, 2009. On March 21, 2010, the House passed H.R. 3590. On March 23, 2010, President Obama signed into law the Biologics Price Competition and Innovation Act (known as the Biosimilars Act or BPCIA) as Title VII of the Patient Protection and Affordable Care Act (PPACA). The Biosimilars Act created, for the first time, legislation to provide an abbreviated approval pathway for the production, sale and use of follow-on biologic therapeutics in the United States (Malkiewicz, 2016; Brougher, 2010). This abbreviated approval pathway for biosimilars was expected to result in the increased investment by companies in biopharmaceuticals (Addison, 2011).

The enactment of BPCIA did not immediately create the new regulatory approval pathway for biologics because specific rules had to be developed by the FDA. Since biologic medicines are complex in their nature and manufacturing process, it took several years before a clear regulatory framework was established and the biopharmaceutical industry was able to move past this period of uncertainty into the new regulatory environment.
Exclusivity Debate

From the very onset of the biosimilars discussion, the issue of data and/or market exclusivity for innovative biologics was front and center. Many stakeholders from the industry and the capital side advocated for longer periods to incentivize innovation, while biogeneric producers and some consumer groups pushed for limited periods of exclusivity as a means of lowering costs.

At an early Senate committee hearing in 2004, Amgen’s Senior VP for Global Government Affairs, David Beier, outlined Amgen’s position on this issue. “Mr. Chairman [Senator Orrin Hatch], as the author of Hatch-Waxman and as a supporter of innovation through other mechanisms such as orphan drug and pediatric exclusivity, you know firsthand the power of strong but fair patents, data exclusivity and trade secrets to spur investment, innovation, and ultimately for breakthroughs for patients. … What do I mean by protection for innovation? In sum, it is the combination of patents, data exclusivity and trade secret protection. Billions of dollars of reasonable, investment-backed expectations rest on the maintenance of these rights. These rights benefit patients by promoting research and development for new breakthroughs. They protect the invention, usually in the form of a product patent, or, often for biotech products, the process. They also protect the pre-clinical and clinical trial data created by an innovator at the cost of hundreds of millions of dollars. This data exclusivity is an integral component of innovation protection. Finally, the proprietary formulas, especially the detailed manufacturing specifications, are protected under Federal law as trade secrets. As an innovator, Amgen does not seek to extend our legal rights beyond the metes and bounds of existing innovator protections. On the other hand, we would be concerned if the FDA seeks to rely on our proprietary data to approve a follow-on product. To respond to Mr. Schultz’ comments, it is true
that the FDA in other analogous regulatory systems relies on the approval of other products. But as he carefully noted, they do not rely on the underlying data of the innovator. Our concern is about whether the agency [FDA] would pierce our trade secrets and knowledge of our manufacturing process and use that information to approve a follow-on product” (Senate Hearing 108-635, 2004).

In March of 2007, the Senate Committee on Health, Education, Labor, and Pensions held a hearing on the proposed bill S. 623 (the so-called Clinton-Schumer bill). One of the witnesses was Dr. Ajaz Hussain, Vice President and Global Head of Biopharmaceutical Development at Novartis – European biotech giant with a significant presence in the U.S. market. In Dr. Hussain’s testimony, data exclusivity issue was front and center. “Protection of intellectual property is the lifeblood of innovation. Strong intellectual property protection, including patents, trade secrets, and confidential information, is essential to promoting innovation that results in new therapies to meet patient needs. However, Novartis believes that, by having a regulatory pathway that allows more rapid and efficient realization of this innovation through greater use of comparability and prior knowledge for second-generation products as well, these IP rights are enhanced not undermined by a follow-on biologics pathway. Moreover, with each follow-on sponsor developing its own independent data package, and not relying on the innovator’s data, we believe these property rights are respected even for those products on which the patents have expired and competition appears imminent. Historically, the biotech industry has established robust patent estates. However, when these patents expire (including patents claiming those PHS Act products for which up to 5 years of patent-term restoration already has been granted under existing Hatch-Waxman), increased competition and access to safe and effective medicines should proceed in the free market. Litigation over patents will still occur, but those litigation
proceedings should, and in fact do not need to be coupled to the regulatory approval process. … Novartis supports a non-patent research incentive such as may be achieved through modeling on EU data exclusivity provisions, more appropriately called market-exclusivity provisions, for innovator biologics approved after enactment of any new legislation, as a way to enhance regulatory certainty for all sponsors (which would be independent of the patent estates). Such an approach would prevent diversion of excess resources being used by either innovators or the sponsors of follow-on biologics on slow and expensive patent litigation, and enable those resources to be dedicated to the development and new and more efficient manufacturing of biologics. … Novartis would support some form of exclusivity for the sponsor of innovator products approved in the future, and used as the reference product for a follow-on biologic, whereby they would not face market competition for a set period post-approval. This could recognize the market uncertainties for these products, and as in the original Hatch-Waxman statute, enable the development of products with limited or no patent protection. Such an exclusivity would encourage the further creation of innovator products” (Senate Hearing 110-375, 2007).

When Dr. Hussain of Novartis was questioned directly by Senator Enzi as to his company specific position on data exclusivity (since Novartis is active in both novel and follow-on biologics), the response was still favoring exclusivity. “We do believe that a balance of incentives for innovators will be important, as we create the new pathway that enables competing, interchangeable follow-on biologics. Indefinite monopolies for innovator products, even when all patents have expired, is not appropriate for biologics, any more than it was for drugs back in 1984 when Hatch-Waxman was enacted. Novartis believes in respect for intellectual property and competition, and believe that both will ultimately benefit patients
through the greater availability of more and better medicines. Competition is the best way to ensure access to cost-effective drugs after patents expire, and we believe that the time has come for the authority to be granted to the FDA to approve Follow-on Biologics. These Follow-on Biologics will compete in the free-market, and newer and better ones will continue to be created, as long as it is to the same consistent, appropriately-high, science-based regulatory standards that apply to innovator products, and as long as legitimate intellectual property is respected. To the extent that market exclusivity can be provided to innovator biologics approved subsequent to enactment of any proposed legislation, we would anticipate being supportive, as we believe this gives a greater certainty to innovators, and as such will be a stimulus to their continued innovation” (Senate Hearing 110-375, 2007).

Senator Michael Enzi expressed concern about the lack of exclusivity provisions and IP protections in the Access to Life-Saving Medicines Act S. 623. “In addition to ensuring patient safety, any follow-on biologics pathway created by the Congress must preserve incentives for research and innovation by ensuring protections for intellectual property and providing data exclusivity for innovative therapies and cures. Unfortunately, the Access to Life-Saving Medicines Act (S. 623), which proposes to create such a pathway, is deeply flawed in all three respects. As Dr. Siegel’s testimony powerfully explains, this bill would jeopardize patient safety in numerous ways. Further, contrary to its title, the bill would eviscerate incentives to develop life-saving new medicines through its one-sided alteration of long-standing patent law in ways that favor follow-on biologics manufacturers, who would be able to restrict and infringe the intellectual property rights of various parties including innovative biotechnology companies. S. 623 also should be opposed for its lack of data exclusivity for innovative biologics. Data exclusivity provisions have served as an incentive for innovation under Hatch-Waxman and are
part of the European system for regulating "biosimilars" (i.e., follow-on biologics). The legislation contains no prohibition on the FDA approving a follow-on product relying on innovator data immediately following approval of the reference product. Devaluing property rights and the absence of data exclusivity disincentivizes the necessary investment for a strong, vibrant pioneer biologic industry, upon which any follow-on market wholly depends” (Senate Hearing 110-375, 2007).

Senator Richard Burr voiced the same concern regarding the importance of exclusivity to reward pioneers of innovation, though he spoke specifically about effects on investment decisions. “I am sorry to see that we do not have a witness testifying on the impact of the Clinton-Schumer bill on the financial viability of innovator biotech companies. If we did have such a witness, I think the witness would say that venture capital for biotech companies would dry up because this bill guts any drive for biotech companies to innovate. Why should a biotech company go through huge clinical trials, manufacturing challenges, studies, etc. to get a biologic approved when the day after approval a follow-on biologic company can send them a letter asking for a list of every single patent that is a part of making that biologic. And after providing that list, the innovator can only sit back and wait for the follow-on biologic company to submit an application at the FDA saying that their product is comparable to the innovator's product – not the same – but comparable. This bill has no data exclusivity for the innovator. There is no patent protection for the innovator. And there is no marketing exclusivity for the innovator. Why should venture capital firms invest in biotech companies if the companies have no guarantee of recouping their research investment?” (Senate Hearing 110-375, 2007)

Later in March of 2007, the House Committee on Oversight and Government Reform met to discuss the biosimilars bills that were being advanced on Capitol Hill, with the specific
focus on H.R. 1038 sponsored by Representative Henry Waxman. The issue of exclusivity as the incentive for innovation was again debated by the members of the committee and witnesses invited to testify. Representative Tom Davis opened the discussion: “Given the high cost of research, development, manufacturing, and regulatory approvals, IP protections are clearly a critical factor for biotech startups when they are securing venture capital and pursuing partnerships with larger firms. … It would be tragic if legislation intended to increase access to medicine would have the unintended result of stifling innovation, preventing the discovery of cures of presently terminal diseases. I hope you would agree with me, Mr. Chairman [Rep. Waxman], about the importance of fostering a vibrant and innovative culture where we encourage our brightest minds and daring entrepreneurs to do the research, provide the investment so that we may someday discover the cure for cancer or Lou Gehrig's disease. Reflecting on the Hatch-Waxman Act, you got it right when you recognized the importance of balancing the twin goals of bringing generic drugs to market while at the same time leaving intact the financial incentive for research and development. One of the keys to this successful balance in that legislation was the guarantee of 5 years of market exclusivity for innovative companies. Incidentally, European Union regulators currently provide 10 years of market exclusivity for European drugs for innovative drugs. Some amount of market exclusivity for the innovator is necessary under any regulatory pathway for follow-on biologics” (House Hearing 110-43, 2007).

Among the witnesses at this hearing in 2007 was the economist Dr. Henry Grabowski, a widely published (and cited in this research) author on economic analysis of intellectual property protections and their effects on innovation levels. Dr. Grabowski submitted written statements and provided oral testimony explaining, based on empirical evidence, how an IP
protection uncertainty affects capital market decisions for emerging private and public biotech firms. “In designing a pathway for follow-on biologics it is also very important that Congress balance price competition and innovation incentives. In this regard, it is important to include in the legislation a data exclusivity period that takes account of the high cost and risk of developing new entities. My statement provides data from a new study that is peer reviewed and co-authored with Joe DiMasi in this regard. The cost of R&D for a representative new biologic is now over $1 billion when one takes account of preclinical and clinical expenditures, the cost of failures, the cost of capital, and process engineering, which is higher for biologics than pharmaceuticals. I understand the bills under consideration have no data exclusivity provisions or patent restoration features for innovators. The fact that there is no data exclusivity provision would allow generic firms to challenge innovators' patents from the date of first marketing approval and to enter the market soon thereafter. The resulting uncertainty in IP litigation would have significant negative incentive effects on capital market decisions for private and public biotech firms with pipelines. Many of these firms are entrepreneurial in nature and have few if any profitable products. The exclusivity period for pharmaceuticals under Hatch-Waxman is 5 years. R&D costs have increased substantially since Hatch-Waxman was enacted 20 years ago. Five years does not provide enough time for firms to recoup the high cost of discovering and developing a new medicine. Break-even returns on R&D for the average new drug and biological product now exceed more than a decade. Since this legislation will essentially define the terms of competition between innovators and imitators for decades to come, it is critical that it maintains strong incentives for R&D investment in new biopharmaceuticals, as well as provide incentives for price competition. A data exclusivity period of at least 10 years in length would recognize the high cost and risk of developing new biological entities and deter patent challengers from
occurring and entering until a more mature phase of the product life cycle. This would also preserve incentives for the development of new indications for existing drugs and harmonize U.S. law with that of the European Union” (House Hearing 110-43, 2007).

In May of 2007, despite the strong support for longer exclusivity term for innovative biologics from the industry, trade associations and finance, there was opposition by follow-on product manufacturers and consumer groups that were concerned with the rising costs and affordability of biologic treatments. Bruce Downey offered his perspective as Chairman of the Board for the Generic Pharmaceutical Association and Chairman and CEO of Barr Pharmaceuticals at the House Committee on Energy and Commerce hearing. He argued that long exclusivity period would negatively affect innovation. “I would argue and I think correctly argue that the pathway for generic pharmaceuticals was the greatest boon to pharmaceutical innovation in history because it forced brand manufacturers to replenish their products in the face of generic competition. And so you look at the statistics, and I didn’t prepare it for today but I certainly could and submit it if the committee wants, the rate of investment in R&D in the brand industry skyrocketed post Hatch-Waxman because of the threat of generic competition. And I think the same will happen here in the biologics business. If there is a generic pathway, you will see increased innovation and increased spending on R&D.” In his submitted statement, Downey asserted that “lengthy, new exclusivity periods for brand companies are not necessary because the law currently provides more than enough incentive to continue innovating. For example, brand companies already get significant incentives, including multiple provisions allowing for patent term restorations, orphan drug exclusivity, and various tax credits. If the brand companies disagree, they are free to come forward and present data to support their argument. Indeed, Representative Waxman has invited discussion on this issue. However, the brands have not yet
come forward with any concrete data that would suggest that additional incentives are necessary. … With these numerous special protections and incentives already available to the biotech industry, a credible argument certainly can be made that Congress need not give these companies additional ways to prolong their monopolies and deny the public prompt access to affordable biological medications. ... Furthermore, any discussion of additional incentives quickly finds the brand industry demanding an entirely unjustified amount of time for data exclusivity. … Despite the incentives that already exist for brand companies to invest in new biological products, in order to obtain a workable pathway for the approval of generic versions of biological products, Barr would support a reasonable marketing exclusivity period for products containing new active ingredients. Barr cannot, however, support filing moratoriums, i.e., provisions that prevent generic companies from submitting applications. H.R. 1956 contains two types of filing moratoriums: one that prevents a generic company from submitting an application for 12 years from the date of brand approval, and one that prevents the submission of an application until FDA completes a formal guidance process – a process that would take years. There simply is no legitimate justification for such provisions, which do nothing but delay generic market entry even on off-patent products that FDA approved more than a decade ago. Consumers and taxpayers need and deserve better” (House Hearing 110-40, 2007).

Despite the active biologics debate on Capitol Hill, no bill was enacted, but it was becoming clear that it won’t be much longer. With the election of President Obama and his lead to enact a healthcare reform, the timing was proper for finally creating a comprehensive biologics act that could be built into the healthcare reform legislation. More versions of the potential biologics bill were advanced and discussed, among which was a bill by Representative Anna Eshoo (H.R. 1548) whose California district included the headquarters of many
biotechnology companies. At the 2009 hearing of the House Subcommittee on Courts and
Competition Policy of the Committee on the Judiciary, the Subcommittee Chair Representative
Johnson declared: “Congress has explored the creation of a generic pathway for biosimilars for
some time, but it wasn’t until this Congress that real momentum has built behind such a
legislative endeavor. … Creation of a pathway for biosimilars has been a contentious issue.
Much of the debate concerning such a pathway revolves around whether the science is perfected
enough to determine if a biosimilar that relies on an innovator’s test data will have the same
health benefits as the innovator drug without additional health risks. Additional concerns center
on the intellectual property protections afforded drug innovators and how the nature of those
protections will impact competition, future biotechnology industry investment and the cost of
biological pharmaceutical products. … The question before us today is how to frame the
intellectual property protections in a pathway for biosimilars that incentivizes the extraordinary
investment required to develop new biologics but does not discourage biosimilar introduction”
(House Hearing 111-73, 2009).

IN 2009, Representative Eshoo’s bill proposed to grant the manufacturers of innovative
biologics 12 years of exclusivity. This proposal was supported by biopharmaceutical firms, but
many consumer advocate groups and biotech companies with significant interest in the follow-on
market found this 12 years of exclusivity to be excessive. Mr. Larry McNeely, a health care
advocate for the United States Public Interest Research Groups explained the opposition to long
exclusivity in his testimony. “So, how should a law strike a balance between access and future
innovation on one hand and the manufacturer’s need to profit from its investment in a great
product? Rather than looking at research from one industry group or another, to find the right
balance, we examined an independent source, the Federal Trade Commission’s report on follow-
on biological drug competition. The report found that the patent system has a proven record of protecting and stimulating biotechnology innovation. In fact, they found in some ways biologic patents are stronger than chemical drug patents. In summary, FTC found that the pioneer biologic drug manufacturers can earn significant revenues many years after follow-on biologic entry, obviating the need for the 12- and 14-year exclusivity period. It is far too long. … Mr. Chairman, we need a strong, vibrant markets for biologic drugs in this country, but we need markets that drive innovation, not those that reward monopoly” (House Hearing 111-73, 2009).

A vast written and oral testimony was offered by Attorney Jeffrey Kushan who was representing the Biotechnology Industry Organization (BIO). His arguments for longer exclusivity were emphasizing the need for stimulating and protecting novel biotechnology innovation. “First, nearly all stakeholders agree that data exclusivity must be part of an abbreviated biosimilar pathway. Data exclusivity is a regulatory mechanism that functions by deferring when biosimilar products can be approved on the basis of the innovator’s clinical data. The differences of opinion that exist now revolve around how long the data exclusivity period should be and how it should relate to continued clinical development of products” (House Hearing 111-73, 2009).

In his submitted written testimony, Attorney Kushan further explained BIO’s position. “BIO supports the creation of an abbreviated pathway for biosimilars to help increase competition among, and access to, the many breakthrough biomedical advancements that have been developed by the biotechnology industry over the past 25 years. In doing so, providing effective intellectual property protection for biological products must remain a central focus of Congressional efforts. … Unquestionably, the business of biotechnology innovation will change once an abbreviated pathway for biosimilar products becomes available. And patent rights, as
they exist in today’s system, simply will not be sufficient to preserve the incentives for development of new biological products and treatments that exist in today’s industry. … First, a substantial period of data exclusivity must be provided for the companies that conduct the clinical testing necessary to bring a new biological product, or a new use of biological product, to market. … In this regard, BIO strongly supports the data exclusivity provisions in H.R. 1548 introduced by Representative Anna Eshoo (D-CA) and supported by a broad bipartisan coalition of more than 125 Members of the House of Representatives, along with a wide range of stakeholders, including the American Association of Universities, the National Venture Capital Association, and scores of patient advocacy groups. … Alternative proposals that provide no or only short periods of data exclusivity – or rely solely on the patent system – ignore the obvious and substantial changes to the biotechnology business model that will occur with the creation of an abbreviated approval pathway” (House Hearing 111-73, 2009).

BIO’s call for longer exclusivity appealed to the financial realities of biologics R&D. “The biotechnology business model requires an environment that, as much as possible, reduces unpredictability in the commercial sector. One important factor in this environment is the guarantee of data exclusivity and effective patent protection. Specifically, by ensuring that the products or services that may eventually be marketed can be protected from unauthorized copying and use, companies can justify risks and making significant R&D investments. Introducing greater unpredictability by inadequate periods of data exclusivity, or by limiting the conditions in which patent rights can be asserted, will adversely affect the business environment that is so crucial to supporting innovation in the biotechnology sector. And reducing this uncertainty has, time and again, proven to be critical to the decision-making process of those providing funding for this research and development, particularly the venture capital community.
… A substantial data exclusivity period is particularly critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and where research and development needed for early-stage or adjuvant cancer therapies, which are more difficult and take longer, generally occur later. The substantial exclusivity provided for the original treatment will encourage and support the risky, complex and expensive further development of the product for these additional indications, and will be critical to bring to market the vibrant pipeline of treatments that can allow cancer patients to live longer and better lives” (House Hearing 111-73, 2009).

Another witness, Mr. Alex Brill of the American Enterprise Institute, expressed a more modest approach to the exclusivity period. “Ultimately, it is a balancing act, promoting innovation by shielding the company from market competitors, and promoting innovation and price competition by allowing market entrance. … However, when thinking about the optimal amount of protection to give an improvement to an existing drug, we must once again return to the basic question of the particular market dynamic. An improvement that enlarges market share would increase profits further, thereby mitigating the amount of needed exclusivity. Furthermore, the more exclusivity that is expected to be attached to a drug for its improvements, the shorter the period that needs to be given to a newly approved drug initially. In my view, the total exclusivity period, including extensions, should be close to 7 years. … I do not take as strong a stand against an exclusivity period as does the Federal Trade Commission. The cost of providing modest additional intellectual property rights to drug originators will likely outweigh the potential costs. Research I conducted demonstrates that an exclusivity period of 7 years is sufficient to ensure that innovator drug companies continue to earn the necessary economic rents. Modeling included in the recent FTC report further extends that model and finds support for the
view that 7 years of market exclusivity will be sufficient. Proposals that establish a long period of market protection will lead to unreasonably large rent for originator drug companies and provide no additional benefit to consumers” (House Hearing 111-73, 2009).

The sponsor of the bill Representative Eshoo argued that the amount of required capital investment is what drove her bill to the side of longer exclusivity. “Biologics are expensive, and they are risky to develop. A recently released study sponsored by the National Venture Capital Association analyzed the relative cost for investors in biotechnology and found that the cost of capital for startup biotech companies is more than double the costs that other companies must pay. These costs stem from long developmental timelines of typically 10 years or more and extraordinary levels of risk. Fewer than 1% of biologics make it to the market. Imagine that. Fewer than 1 percent. And the large amounts of capital required to support this development are at the other end of the scale” (House Hearing 111-73, 2009).

To hear directly from the venture capital side, National Venture Capital Association was represented by witness Jack Lasersohn who outlined the financiers’ position on the matter. “It is probably not well-known that the venture community is the primary founder and funder of biotechnology in the United States. Indeed, it is not an exaggeration to say that venture capitalists founded the biotechnology industry in the 1970’s and 1980’s. For example, both Amgen and Genentech were founded by venture capital firms, and even today supply nearly all of the capital for early-stage biotechnology companies. In turn, our entrepreneurial biotechnology companies discover and develop the overwhelming majority of new biological drugs in the world. I cannot emphasize this point enough. The last time we looked at this, these companies were responsible for 80 percent of the new biological drugs in the entire pipeline of biotechnology development. While we have been actively involved in this behind the scenes, we
have in fact not participated in testimony before the Congress before, and we did not have an
opportunity to testify to the FTC. If we had, we would have said the following: We absolutely
support a well-designed FOB [follow-on biologics] process that will ultimately lower prices and
improve access for biologicals for consumers while preserving investment in discovery and
development of revolutionary new biotechnology drugs. The FOB system endorsed by the FTC
[no exclusivity, only patents] will absolutely not accomplish these goals. Instead, it will result in
a dramatic reduction in our ability to fund new drug discovery, leading to a Pyrrhic victory in
which we have very cheap versions of old biologics and a vast reduction in the pipeline of new
drugs which have the potential to revolutionize medicine. Both goals are important. Now, this
may sound like a rehash of arguments against HatchWaxman in 1984, but this really is different.
First, the current biotechnology industry bears no resemblance to the pharmaceutical industry in
1984. Most small-molecule drugs were discovered by large pharmaceutical companies in those
days, and still are today. As I said, in contrast, virtually all new biological drug development
today are discovered by small, private, VC-funded start-ups. This is an absolutely critical
difference. These companies have no cash flow and depend entirely upon us for financing. We in
turn invest in these incredibly risky, illiquid and very long-term investments, and usually lose
money on about 50 percent of them. To justify this risk and time, we must produce a return that
is much higher than you can get from less risky investments and much higher than large
biotechnology and pharmaceutical companies need to make. If we don’t get those returns, in turn
our investors will not give us money to invest in biotechnology, and indeed, that is already
beginning to happen. This return is our cost of capital and is much more than the 10 percent that
has been assumed by supporters of other more aggressive FOB systems. In fact, it is over 20
percent, as a new Harvard and Boston University report showed that was just published last
week. All of the published models demonstrate that with a 20 percent cost of capital, or even a blended cost of capital of 10 to 12 to 15 percent, we cannot break even on these enormously risky investments if generic follow-on biologicals competition can enter the market immediately or as little as 7 years after our drugs. If we cannot break even, we cannot invest” (House Hearing 111-73, 2009).

Bruce Leicher, Senior VP and General Counsel at Momenta Pharmaceuticals, spoke against extensive exclusivity and protections because Momenta is both an innovator and a biosimilar producer. “Momenta also offers a unique perspective in this debate. We are a biotech company that develops both generic and novel therapeutics. … Notably, biologics generally have more market exclusivity during their brand life than drugs. Add to this 5 years of patent extension, and I have to ask, why should biologics need more data exclusivity than drugs to recoup investment? Beyond that, brand innovation and competitiveness are motivated by limited data exclusivity as well. Extended data exclusivity will attract capital, but the wrong kind. It will promote low-risk, non-innovative development, and make biotech in the long run far less competitive. Biotech funding should be directed to innovative, patentable new cures. Or is our goal to offer brand exclusivity profit for me-too products?” In his submitted statement, Leicher wrote: “Aside from robust patent protection, there is a far more important reason to appropriately limit data exclusivity: to incentivize innovation and future competitiveness. Consider the effect of extended data exclusivity on R&D investment decisions. The issue is not whether data exclusivity will trigger substantial R&D investment, but rather what kind of R&D it will promote. Will funding be directed to innovative, patentable discovery of new cures – the hallmark of biotechnology companies in the 1980s and 1990s? Or, will it instead reward de-risking of product development portfolios by offering exclusivity for the development of non-
innovative or “me too” products? From an investment perspective, financial investors are agnostic to the degree of medical need and will certainly drive us toward the lower risk, higher reward development that have extended data exclusivity. By extending exclusivity beyond patent life, we put truly new innovative R&D further at risk, which will delay urgently needed efforts to discover cures for so many unmet needs. … And what I think everyone is missing is, if we provide an excessive exclusivity period, we are going to create a huge incentive for the biotech industry to derisk their portfolios, because now, without having to innovate, without having to get patents, you can get a product developed and, by virtue of getting it approved by the FDA, guarantee 12, maybe 14 years of exclusivity. … It is a little puzzling to me, in 2009, you know, in the year that GM declared bankruptcy and perhaps declared bankruptcy because it stopped innovating in the 1990’s and focused on high-margin SUVs as opposed to innovative cars—and I am concerned, having lived in biotech for 20 years, that we are going to push biotech from the innovative scale and the leadership in the world to the non-innovative scale” (House Hearing 111-73, 2009).

Additionally, Bruce Leicher disagreed with claims that biosimilar producers are not innovators. “We really probably just disagree with the comment that the follow-on biologics industry is not an innovative industry. In fact, that is exactly what we are doing at Momenta and, we believe, at other companies. And that that data exclusivity actually works against that innovation, both on the brand side and on the innovator side. Let me just take a minute to say how. If you set up an excessively lengthy data exclusivity period, it is great from an investor point of view because it allows you to invest in lower-risk development activities, and that is what is being talked about when people are saying biosimilars have a patent loophole. If you invest in developing the second, third, and fourth version of an existing mechanism of action, all
the hard science to discover the mechanism of action has already occurred. And what you are doing is essentially a drug development program, and that is a much lower-risk product. And you are not developing a new cure. And that was the beauty of Hatch-Waxman. What Hatch-Waxman did was it said to the brand industry, stick to your knitting, go out there and find new cures and get strong patent rights that lets you get the exclusivity you need. And it said to the generic industry, apply your science to find out how to make generic copies so that they can deliver affordable products that perform what the maturing biotech products today should be able to do in years to come. And if we are shortsighted enough, and this is what concerns us, to pass a law that assumes that we are only going to have biosimilars and assumes that it is not possible to advance this science, then we are going to make ourselves captive to what is happening in China because they will move ahead of us, and we will be competing with China. If we build our technology base in the United States and actually own the science here in our biotech industry for innovative biogeneric products, we really create an opportunity that keeps us ahead of the rest of the world” (House Hearing 111-73, 2009).

Venture capital representative Jack Lasersohn disagreed: “I, with respect to the issue that increased generic or FOB competition, or that those competitors will be innovators, is something I have to admit I have heard over and over again, and I don’t understand. It is absolutely the case that the FOB companies will produce price reductions, which may benefit consumers, but they have never been innovators. And I don’t think they are suggesting, in fact, none of the ones I talked to suggest there are going be innovators in developing new drugs. That is my first point. Innovation will continue to come from branded, innovative, small entrepreneurial VC-backed companies” (House Hearing 111-73, 2009).
In his submitted statement, Larry McNeely of the United States Public Interest Research Groups reiterated the point that patent protection is sufficient for IP protection for biologics. “All the available evidence is that the patent system provides adequate protection for innovator biologics and provides an adequate incentive to raise capital for investments everywhere in the world. I recognize that the biotech companies argue that 14 years of exclusivity is necessary for them to invest in these products. But it is obviously in their interest to get the maximum amount of exclusivity to maximize their profits. … Thus it is important to look to an independent source to evaluate the validity of the biotech industry’s argument that 14 years is essential to create a sufficient incentive for investing in these products. A recent study by the Federal Trade Commission provides a very helpful evaluation. … The FTC’s conclusions are important because chemical treatments flourished without the 12 or 14 years of exclusivity that the biologics manufacturers are demanding. … The basic compromise that led to the enactment of Hatch-Waxman was not the 5 years of exclusivity. Instead the brand companies demanded and received patent extensions to compensate patent time lost as a result of the FDA drug approval process, which includes both the time needed to test the drugs and the time the FDA takes to approve products. Under Hatch-Waxman, companies are eligible for a patent extension of up to 5 years as along as the extension does not extend patents to more than 14 years. Importantly, these patent extensions already apply to biologics. Thus, even though Hatch-Waxman did not establish a generic program for biologics, it did give biologic innovators the same patent extensions that it gave to the chemical brands. Rewarding yesterday’s innovation too much can prolong the day that we see the next life saving biologic drug. By granting additional protection to biologic products, above and beyond the manufacturer’s patent, will not only keep the drug expensive and out of reach of many Americans. We strip away the incentives to develop the next generation of
life-saving drugs. … Proponents of more protection for pioneer drugs claim that biologics are different from chemical drugs. They argue that the investment needed in sophisticated manufacturing and development of biologics would render patents or even Hatch-Waxman style 5 year exclusivity periods inadequate. In fact, if their position was true, we should first consider extending protection to industries who face the greatest cost of capital. But that would mean providing monopoly power to investing in several industries with higher capital costs long before we got around to biotechnology. These dubious arguments serve primarily to defend and preserve the monopoly position enjoyed by a few powerful manufacturers. … So when it comes to encouraging innovation, we can only conclude that the industry is selling a cure that’s worse than the disease. Fundamentally, the choice before Congress this year is whether to reward yesterday’s life saving innovation or tomorrow’s” (House Hearing 111-73, 2009).

Jack Lasersohn, representing venture capital, argued with proponents of short exclusivity. “I can tell you, despite the what the FTC argues, that I and other VCs cannot rely on patents alone to continue to make investments in early-stage biotechnology companies. The data exclusivity period of 12 years that we are requesting is merely insurance against the possibility the FTC and the proponents of more radical FOB systems are wrong in their speculations about how strong patents will be. If they are correct, patents will give us 12 years anyway and the data exclusivity will be completely irrelevant. But if they are wrong, the data exclusivity will simply give us the same period to recoup our investments that the [small-molecule] pharmaceutical industry already has under Hatch-Waxman. This seems to us like a prudent compromise to avoid the enormous unintentional — unintended damage to our entire entrepreneurial biotechnology industry” (House Hearing 111-73, 2009).
Bruce Leicher of Momenta Pharmaceuticals submitted Momenta’s statement provided to the FTC in which they expressed their position that a more modest 7-year exclusivity was more appropriate and justified. “We agree with most panelists that anticipated market share for Biosimilars and for Biogenerics will not interfere with continuing and robust innovator brand sales after the expiration of a data exclusivity period – particularly during the first few years following expiration. Consequently, the breakeven point will be significantly earlier than 12.9 to 16.2 years posited by Professor Grabowski. We agree with Professor Brill that appropriately accounting for these continuing sales suggests that a data exclusivity period of 7 years is sufficient to provide a return on investment. This is because he estimates they will have at least 10 years of revenue (3 years beyond a 7 year data exclusivity period) which is a much more realistic assumption. It is important to note that “breakeven” is not the point at which profits begin to be earned. Rather it is the point at which the expected rate of return (i.e., profit) from an investment along with return of principal is recovered. Moreover, this is only the breakeven point, and we believe that sales of the innovator brand product will continue well beyond this 10 year period as well. … The proposals for 12-14 years of exclusivity, however, in light of the significant patent protection available to biologic products, are not needed to encourage new product innovation. A 12-14 year data exclusivity period would serve instead to extend the time for launch of competitive Biosimilar or Biogenic products and would create a significant disincentive to investment and defer the economic benefits of follow-on biologic competition, and in particular, the timely market entry of more affordable and potentially life-saving follow-on products” (House Hearing 111-73, 2009).

Attorney Kushan outlined BIO’s view on patents vs. exclusivity issue. “When you look at the statistics, that period is around 12 to 14 years at this point. So for small-molecule drugs, you
are seeing generic competition start 12 to 14 years. Now, the big difference when you shift over into the biosimilar environment is that there’s a loophole that has been created. And that loophole is simply, unlike Hatch-Waxman, where it is prohibited to do this, a biosimilar manufacturer can essentially skirt the patent rights but then get the benefit of the clinical data to get on to the market much faster. And it’s that character of the biosimilar product that creates the risk that is answered and addressed by a data exclusivity period that essentially provides a backstop for the patent rights. … The concern that is driving the call for a stronger data exclusivity period is precisely the uncertainty that exists that we can, as innovators, know that our patent rights will give us that protection, and that’s essentially the major difference. You have in the Hatch-Waxman system, the ability to kind of get around the patents. You are similar enough, but not so similar to not rely on the clinical data.” Jack Lasersohn explained this point in more details: “The second difference is how patents work in this system as compared to the generic biological system. The difference is obvious and simple. Under Hatch-Waxman, a simple composition-of-matter patent gives you enormous certainty that you can preclude generic competition during the life of the patent. It gives you a reasonable period to recoup your investment. Under an FOB system, you have no such certainty, because an FOB does not have to be identical with the approved drug. So a composition-of-matter patent, which is the strongest type of patent, may be completely irrelevant and unprotected” (House Hearing 111-73, 2009).

Representative Brad Sherman called on his colleagues to support Eshoo’s bill and summarized his take on the issue of exclusivity: “There has been talk about the biotechnology industry being able to recover its sunk costs on a particular drug. And if they can’t recover their sunk costs on that drug, obviously, there will be no more innovation. I think this massively understates the situation, because the vast majority of drugs are—the vast majority of drug
development projects are failures. And even when they lead to success, they may be outmarketed by some other cure for that disease. So unless an innovator is able to recover double, triple or quadruple its sunk costs on the successful drug, we can basically pack up this industry and say we are not going to have any more innovation” (House Hearing 111-73, 2009).

In July of 2009, the National Coalition on Health Care (NCHC) sent a letter to the Chairman of the Senate Committee on Health, Education, Labor, and Pensions, Senator Ted Kennedy and the Committee's ranking member, Senator Michael Enzi. The NCHC describes itself as a non-profit and non-partisan group comprised of over 70 organizations that employ or representing about 150 million Americans and work together to improve America's healthcare. In its letter, the coalition stated its opposition to long exclusivity proposals. “In connection with the Committee's consideration of a generic biologic program, we would like to highlight the issue of exclusivity for innovator products. Some of the bills that have been introduced would provide that innovator biologics would be entitled to 12-14 years of exclusivity, a period of time during which generic competition would be barred. We urge you to oppose generic biologics legislation that contains excessive periods of exclusivity or that contains other unnecessary and significant barriers to generic, biologic competition. … The five year period of exclusivity provided in H.R. 1427 follows the Hatch-Waxman model and is the appropriate period of exclusivity. An unnecessarily long period of exclusivity would significantly delay the entry of generic versions of biologics and thus would delay the savings to the health care system from a generic biologic program at FDA. It would also diminish the incentives for other companies to continue innovating, actually resulting in less innovation over time. Prescription drugs accounted for almost $300 billion in 2008 and biologics accounted for almost $45 billion. Many of the most expensive drugs on the market today are biologics and the national bill for biologic drugs is
expected to grow significantly in the coming years. Increased use of generic drugs have dramatically reduced drugs costs for chemical drugs and have the potential to do the same for biologic drugs. For this reason, we urge you to include the key provisions of H.R. 1427 in national health care legislation. Our nation is experiencing a massive health care cost and economic crisis. Increasing the availability of generic biologics will be a critical element of a comprehensive necessary health care cost containment strategy” (Patent Docs, 2009).

**Purpose and Goals of the BPCIA**

In 2004, at the time when European Union was enacting its biosimilars regulations, there was an emerging concern about the innovation levels in new therapeutics in the U.S. In its 2004 report, the FDA stated: “Today’s revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not quickly yield more effective, more affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications has also decreased. In contrast, the costs of product development have soared over the last decade. Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Developing products targeted for important public health needs (e.g., counterterrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging” (FDA, 2004).
The public policy behind the Biosimilars Act was to provide incentives that stimulate continued biotechnology innovation while expanding access to important biological therapeutics by maintaining the same important requirements of all biologic sponsors of a demonstration of safety and efficacy to treat important ailments (Simmons, 2010). In crafting the legislation, U.S. lawmakers were attempting to strike a balance between two competing but synergistic objectives: stimulating biotech innovation and allowing less expensive follow-on biologics to eventually enter the market. U.S. Representative Nathan Deal expressed this idea clearly when he addressed his colleagues at the 2007 hearing of House Committee on Energy and Commerce. “One of the most difficult aspects of this issue is to provide a balance between incentives for innovation while allowing similar lower-cost products to come to market. Hatch-Waxman provides these incentives for innovation in the form of market exclusivity and patent term restoration. As we strike this balance, I believe we do need to provide some period of market exclusivity as an incentive for innovation while ensuring that the judicial process and patent litigation can be resolved in a fair and timely manner. Other countries are already acting on this issue, and the Congress needs to provide a pathway for the approval of follow-on biologics in this country. We have an opportunity to provide patients access to a lower cost alternative for their needed medications. While the fund is unclear, the degree of savings that could be achieved with a follow-on protein product for status quo is no longer acceptable and ignores the possibilities presented by generic biologics. By no means does the committee face an easy task. This is a complex subject, and we must wrestle with a number of scientific, regulatory, intellectual property, and safety issues. However, I do believe we can resolve and balance these issues in order to provide patients' access to safe, lower-cost medications” (House Hearing 110-40, 2007).
The BPCIA is among the most important pieces of legislation impacting intellectual property rights of biomedical researchers and biopharmaceutical producers in U.S. history. It should have a direct impact on IP rights of international biologics manufacturers seeking to sell biological products in the U.S. (Simmons, 2010). The Act was implemented with the understanding that biosimilars are not a generic version of the innovator products, and therefore a demonstration of therapeutic equivalence based on pharmaceutical equivalence and bioequivalence is not sufficient (Simmons, 2010).

Pharmaceutical companies exploring innovation in the more complex and expensive biologics market may now have more financial incentive to innovate and develop new therapies from the additional rights granted by the Biosimilars Act (BPCIA), which was not available prior to 2010. This policy change may lead to the development of products that would not have been developed without the added incentive of market exclusivity and increased profits (i.e., monopoly pricing) during this period.

Terminology (according to FDA)

The Affordable Care Act (ACA) of 2010 amended Section 351 of the Public Health Act to establish a new abbreviated licensure pathway for follow-on biologic products that are shown to be biosimilar to or interchangeable with a reference biological product licensed by the FDA (Pinto et al., 2015). The Public Health Service Act (PHSA) of 1944 defined a “biological product” as a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product. The BPCIA has amended this definition to include proteins (except chemically synthesized polypeptides) and links the definitions of biologics to prevention, treatment and cure of a disease (Davis, 2013).
Before discussing specific provisions of the Biosimilars Act pertaining to licensing and
exclusivity, it is essential to understand the terminology that is used by the FDA to differentiate
between various biologic drugs. Biosimilars are not merely generic versions of the biologic.

*Biological reference product* – an already FDA-approved original “pioneering” biologic
medicine made from living organisms (including humans, animals and microorganisms) that are
manufactured through biotechnology, derived from natural sources or, in some cases, produced
synthetically.

Follow-on biologics are categorized as either *biosimilars* or *interchangeable* biologic
drugs.

*Biosimilar* – a biologic drug that is not identical to the previously approved reference
product but is substantially similar to it (except for minor differences in clinically inactive
components), so that the same clinical outcomes are expected (Silber, 2013). It must be a
“biological product that is highly similar to the reference product notwithstanding minor
differences in clinically inactive components,” and FDA requires that there be no clinically
meaningful differences between the reference product and the biosimilar in terms of safety and
effectiveness (Simmons, 2010).

*An interchangeable biologic*, in addition to meeting the standard for a biosimilar, must
produce the same clinical results in all patients as a reference biologic. The sponsors of a follow-
on biologic that seeks to be classified as interchangeable must demonstrate that switching from
the reference drug to the follow-on biologic (or alternating between the two) carries no greater
risk than continuing to take the reference product without interruption (Silber, 2013).
Specific Provisions of the BPCIA

Provisions Pertaining to the Designation as a Biosimilar or Interchangeable Biologic

Like the pioneering biologic product, the biosimilar (i.e., follow-on biologic) requires an application seeking FDA approval. The FDA scientific standards often decide how much biopharmaceutical companies need to spend to get a biosimilar approved. While the BPCIA outlined the general pathway for biosimilars approval, the FDA developed specific requirements (Overley, 2016).

In their application for a biologic drug to be licensed as biosimilar or interchangeable, applicants must meet five broad requirements to demonstrate biosimilarity. These five requirements are:

1) Ability to demonstrate that the new drug is substantially similar to the reference product based on data derived from:
   - analytical chemical studies that show that the new drug is “highly similar” to the reference product;
   - animal studies including assessments of toxicity;
   - a clinical study (or studies) that prove safety, purity and efficacy.

2) The applicant must show that the mechanism of action of the new drug mirrors that of the reference product. However, the extent of this requirement is limited to what is identifiable since these mechanisms are often initially unknown.

3) Biosimilar and the reference product must be labeled with the same conditions of use.
4) Biosimilar’s dosage, administration route and strength must be the same as those of the reference product.

5) Applicant must show that the manufacturing, processing, packaging and storage facilities meet the standards to assure safety, purity and potency of the new drug.

There are additional requirements for applicants that want to have their biologic product be classified as *interchangeable*. Since the designation of interchangeable offers additional benefits of exclusivity and automatic substitution for reference product in pharmacies (both of these benefits are not available to mere biosimilars), the sponsor of the application must meet all of the above requirements, plus the additional requirement to show that this new interchangeable drug is expected to produce the *same* – not “highly similar” – clinical result in patients. Furthermore, the risks of safety and diminished efficacy for the interchangeable drug must be no greater than those of the reference product (Overley, 2014).

*Provisions Pertaining to Exclusivity*

*Delay of Market Entry*

The BPCIA is a significant policy change for the biopharmaceutical industry because, like the Hatch-Waxman Act for traditional drugs, it provides innovators of biologics with market exclusivity (independent of exclusivity granted by patent protection) by delaying the market entry of generics. This delay is accomplished by two important provisions:

1) An application for the approval of a biosimilar cannot be submitted until 4 years after the date when the reference product was first licensed (Simmons, 2010).
2) The BPCIA provides the manufacturers of new biologics products with 12 years of exclusivity because it cannot grant final approval to the manufacturer of the biosimilar until a minimum of 12 years from licensing of the reference product (Muller & Shea, 2010).

Therefore, generic biologics are delayed from entering the market, and the innovator firm has a longer period of market exclusivity (granted by the FDA) to recoup their initial investment. These two rules do not apply to licensure for a supplement to the reference biologic product or to the approval of modifications made by the manufacturer of reference product regarding administration route, dosage, strength or biological structure.

In addition to protecting the inventor of the pioneering biologic, the BPCIA also protects the first approved interchangeable-biosimilar. No follow-on product may be designated as interchangeable until one of four possible conditions is met:

1) 1 year passes from the first commercial marketing of the first interchangeable;

2) 18 months pass after the final decision or dismissal of a patent infringement litigation to prevent marketing of the interchangeable;

3) 42 months pass after the initiation of an ongoing patent infringement suit;

4) 18 months pass after the approval of the first interchangeable, assuming no infringement suit has been filed. It is important to note that the last condition prevents license holders of interchangeable biologics from strategically using their licenses to preclude other companies from entering the market.
However, many analysts think that most biopharmaceutical companies will not find these provisions useful. Rather than applying to all biosimilars, they exclusively apply to interchangeable follow-ons, which is anticipated to be a very difficult designation to obtain, and the likelihood of this protection having a significant impact is predicted to be low (Timmis, 2015).

Data exclusivity

The FDA prohibits generic drug makers from obtaining data on drugs targeted for copying until 5 years after they have been approved (Pipes, 2008). The applicant is able to rely on certain existing scientific knowledge about the safety and efficacy of the approved original drug in their application for approval (Rucker & Wolman, 2009). Under the BPCIA, a 351(k) application for biosimilar may not be submitted to FDA for review until four years after the date of first licensure of the reference product. This 4-year wait-to-file period acts as a data exclusivity period (Addison, 2011). After four years, a developer may file an application for a biosimilar, but such a biosimilar application is ineligible for the FDA approval until the 12-year market exclusivity period has elapsed.

Additional hurdle

In addition to delay to market entry and data exclusivity, the Biosimilars Act requires that after filing an application with the FDA, the applicant for a biosimilar must provide the reference product sponsor (i.e., the inventor of the approved pioneering biologic) with a copy of the biosimilar application and the description of the manufacturing process used for production. The reference biologic’s sponsor is entitled to request additional information from the sponsor of the biosimilar. The biosimilar’s applicant must respond within 60 days, and the amount and nature of the requested information are not limited by the Act (Simmons, 2010). The request for detailed
information can include proprietary details of the manufacturing process that could potentially unduly prejudice the biosimilar’s applicant (Simmons, 2010).

**Parallels and Differences with the Hatch-Waxman Act**

Some discussions of the Biosimilars Act, particularly the earlier ones, considered the new approval pathway for follow-on biologics to be analogous to the Hatch-Waxman approval process for generic small-molecule drugs (Davis, 2013). However, because of the differences in regulatory approval for generic drugs and biosimilars, the BPCIA and the Hatch-Waxman Act should not be analogized as they create fundamental, different expectations for the regulatory filings. The new pathway for biosimilars does not set forth a different or lesser standard than that required of an innovator biologic (Simmons, 2010). Nevertheless, the pace of FDA approvals for biosimilars is expected to increase.

As new biosimilars are brought to market, the number of high-stakes biologics-biosimilar disputes is expected to increase. Economics speculate that the traditional economic analysis used for brand–generic disputes under the Hatch-Waxman Act, while still having some applicability, will not be sufficient in the new biopharmaceutical industry (Malkiewicz, 2016).

The BPCIA provides a complex system for resolving patent disputes between the reference product and follow-on manufacturers. It is important to point out that the patent dispute provisions of the BPCIA include a unique requirement for confidentiality of the exchange of information between the biosimilar applicant and the reference biologic sponsor regarding patent rights. The Hatch-Waxman Act, by contrast, requires public disclosure of patents, which are then included in the Approved Drug Products with Therapeutic Equivalence
Evaluations (known as the “Orange Book”). However, because there are no public disclosure requirements for biologics, there is no equivalent record. This difference is critical because unlike small-molecule generic drug manufacturers, follow-on biologic producers are not able to determine what patents they might be inadvertently infringing upon during the development of their biologic product (Simmons, 2010).

The first step of the information exchange is known as the patent-exchange step. After applying for a biosimilar license, the applicant must submit a copy of the application to the reference product manufacturer. In exchange, the reference product manufacturer must give the applicant a copy of all relevant patents that may be infringed. If the list does not include a relevant patent, the reference drug manufacturer cannot later sue for that patent. Due to the nature of biotechnology, it is likely that this list of patents will include numerous references, including claims directed at methods of manufacturing biological products. In contrast, the Hatch-Waxman Act does not permit the listing of patents directed to methods of manufacturing of drugs listed in the Orange Book (Simmons, 2010). Additionally, in contrast to the mechanisms specified in the Hatch-Waxman Act, the reference product license holder must provide a list of patents that it is prepared to license to the biosimilar applicant (Silber, 2013).

The biosimilar applicant then delivers a rebuttal list of their own relevant patents, as well as a claim-by-claim analysis of the reference biologic manufacturer’s list where the applicant explains in factual and legal terms how it is not infringing. For example, the patents are invalid, unenforceable or that the applicant does not intend to commercialize the biosimilar product in the U.S. before the date that all asserted patents expire (Simmons, 2010).
The last step of the information exchange requires the reference-product manufacturer to refute the applicant’s rebuttal within 60 days, asserting on a claim-by-claim basis how, in the opinion of the sponsor, the patents at issue are indeed likely to be infringed by the biosimilar applicant (Simmons, 2010).

The described patent-exchange mechanism for information under the BPCIA is another important reason to distinguish between the Hatch-Waxman Act for small molecule drugs and the Biosimilars Act for biologics.

**Market Competition in Biologics vs. Small-Molecule Drugs**

The Hatch-Waxman Act has been very successful at reducing the prices of traditional small-molecule drugs. The Hatch-Waxman Act resulted in a rapid shift to generics that produced substantial cost savings to healthcare payers and reduced out-of-pocket expenses for patients. Branded small-molecule drugs lose, on average, more than 80 percent of their sales volume within a year of the introduction of a generic. Additionally, generics sell for a price discount of greater than 75 percent compared to the branded molecule (Aitken, 2016).

Because of much more affordable prices, more Americans in need of therapeutics have access to essential medications. Therefore, it is not surprising that Congress somewhat modeled the BPCIA after the Hatch-Waxman Act. However, compared to the Hatch-Waxman Act, many differences in these two legislations, as well as inherent differences between pharmaceuticals and biopharmaceuticals, will likely make the BPCIA much less effective at reducing prices for biologic drugs.
Biosimilars are different than small-molecule generics and their acceptance and costs in the market are expected to vary. It is predicted that biosimilars, on average, will achieve a penetration rate of less than 50 percent. The price discount is expected to be much more modest at around 15 percent (Grabowski, Long, & Mortimer, 2011). When testifying in 2007 in front of the House Committee on Oversight and Government Reform, Dr. Grabowski said: “Based on our analysis, we conclude that the cost of entry will be significantly higher for follow-on biologics than generic drugs. We expect fewer firms will enter, and average prices will decline less for follow-on biologics. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the Government and to other payers” (House Hearing 110-43, 2007).

<table>
<thead>
<tr>
<th>Share of Sales</th>
<th>Price Discount</th>
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<tbody>
<tr>
<td>Generic Drug – Average</td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>Granix (quasi-biosimilar Neupogen)</td>
<td>5 – 10%</td>
</tr>
<tr>
<td>Zarxio (biosimilar Neupogen)</td>
<td>~ 10%</td>
</tr>
</tbody>
</table>

Table 1. Comparison of U.S. Biosimilar and Average Generic Drug, Six Months After Launch (Grabowski, Long, Mortimer, & Boyo, 2016).

The disparity experienced with respect to market penetration and price discounts for biosimilars compared to generic small-molecule drugs is not surprising. Biologics are derived from living organisms and are substantially more complex than traditional small-molecule drugs. Therefore, their production costs are significantly higher than for small-molecule drugs due to various scientific and manufacturing challenges. These increased costs and risks associated with developing and producing biosimilars approaches those of developing an innovative drug. It is more difficult to characterize the structure of biologic drugs, and development and production are more susceptible to variation (Frois, Mortimer, & White, 2016). These obstacles increase the
barriers to entry and therefore reduce competition and impact higher drug prices. For example, Novartis claims that the company, on average, spends about $200 million and requires 7 years to develop a new biosimilar product (Shea, 2011). Therefore, biosimilar competition may be more comparable to the brand–brand drug competition than for the brand–generic drug competition (Frois, et al., 2016).

Another important concern for follow-on biologic manufacturers is that the BPCIA’s interchangeability standards that allow automatic substitution (i.e., the main driver of price reductions) are exceedingly difficult to meet. The FDA requires additional studies and testing to establish interchangeability between the biosimilar and the reference biologic product. The biosimilar must be shown to produce the same physiological response in patients without any impact on the safety and efficacy. Because of the need for additional time and money for such testing, it is expected that interchangeability is not expected to be common for the launch of a biosimilar (Wilson, 2015).

Manufacturers of brand-name biologics have lobbied legislators for the introduction of laws that would limit the adoption of follow-on biologics. Their argument relies on safety concerns to demand a more rigorous review of the substitution. The manufacturers advocate that only interchangeable biologics should be substituted and favor state bills that require patient consent for substitution and for the pharmacist to inform the patient’s physician if a substitution has been made (Dolinar, 2012). In the absence of a designation as interchangeable, pharmacists are not able to automatically substitute a biosimilar for the innovator drug. Because of the variation between the innovator drug and the biosimilar, the FDA will unlikely approve many biosimilars as interchangeable with the reference biologic (Frois, et al., 2016).
For almost two decades prior to the enactment of the BPCIA of 2009, Hatch-Waxman brand–generic small-molecule disputes have been common for the pharmaceutical industry. Now a new and highly anticipated biologic–biosimilar competition is starting to unfold (Malkiewicz, 2016). This new competition has significant economic ramifications.

As of July 2015, there were 57 biosimilars in the U.S. The FDA Biosimilar Product Development Program referencing 16 innovator biologics (Woodcock, 2015). This potential widespread introduction of biosimilars is one of the most significant events within the drug industry in decades; many of the top-selling biologics will be affected over the next few years (Frois, et al., 2016).

At the end of 2016, the FDA approved three biosimilars for sale in the U.S.:

- Zarxio (reference biologic - Neupogen) in March 2015
- Inflectra (reference biologic - Remicade) in April 2016
- Erelzi (reference biologic - Enbrel) in August 2016

<table>
<thead>
<tr>
<th>Innovator Brand</th>
<th>Biosimilar Manufacturer</th>
<th>2014 Global Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>Amgen</td>
<td>$13.0 B</td>
</tr>
<tr>
<td>Lantus</td>
<td>Eli Lilly</td>
<td>$8.2 B</td>
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<tr>
<td>Rituxan</td>
<td>TBD</td>
<td>$7.4 B</td>
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<tr>
<td>Avastin</td>
<td>Amgen/Allergen</td>
<td>$6.8 B</td>
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<td>Herceptin</td>
<td>Amgen/Allergen/Synthoon and Pfizer/Hospira</td>
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<tr>
<td>Neulasta</td>
<td>Apotex and Novartis/Sandoz</td>
<td>$4.6 B</td>
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<tr>
<td>Lucentis</td>
<td>Pfizer/Hospira/Pfenex</td>
<td>$4.3 B</td>
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*Table 2. Selected biosimilars currently being developed for the U.S. market and global sales of the innovator biologic (Frois, et al., 2016)*
Commentators predict that the economic tools and analysis used for pharmaceutical competition developed during the decades of brand–generic Hatch-Waxman disputes (e.g., Lipitor-Zocor) for small-molecule drugs will be useful when applied to biologics–biosimilar competition in BPCIA disputes (Malkiewicz, 2016). However, it is anticipated that economists will likely rely more on analysis developed in the context of the small-molecule brand–brand, brand–branded generic and biologic brand–brand competition, rather than analysis of the small-molecule brand–generic competition alone (Malkiewicz, 2016).

The first biosimilar that became available in the U.S. on March 6, 2015, was Sandoz’s Zarxio for Amgen’s Neupogen (filgrastim) (Pinto, et al., 2015). After the first four months of the launch of Zarxio, it had drawn down only 24 percent of Neupogen’s prescription volume. This is compared to a typical 75 percent penetration of a brand’s volume for the same time period after a small-molecule generic entry (Greenberg, 2016). From the Neupogen–Zarxio comparison, the competition for biologics–biosimilars is more like a brand–brand competition scenario rather than brand–generic competition in the small-molecule pharmaceutical market (Shea, 2011).

Preferential formulary status is another mechanism by which small-molecule brands lose sales and profits after generic entry, where reimbursement and co-pay incentives become available for generics (Malkiewicz, 2016). It is predicted that biosimilars will not receive such reimbursement and co-pay incentives because they do not meet the definition of “generic” or “multiple source” drugs under the Medicare and Medicaid programs. The Center for Medicare and Medicaid Services has determined that biosimilars will be treated as “single source” drugs and are subject to separate coding, higher co-payments for beneficiaries and higher Medicaid rebate obligations for manufacturers than for innovator products reimbursement (Scherb, 2011).
Furthermore, regulatory differences related to biosimilars and generic naming conventions and labeling regulations compared to their reference products may further inhibit a biosimilar from attracting brand sales (Dienes, 2015). In addition to the drug’s proprietary brand name, drugs also carry a non-proprietary active ingredient name (Hawana, 2015). The issue is whether or not the follow-on biologic should include the same non-proprietary name as the reference drug. Concerns about the safety and efficacy are heightened by physicians and patients when a drug has a different nonproprietary name than the branded drug (Silber, 2013).

Biosimilar manufacturers must use distant brand names for their products, which increases costs associated with marketing and sales to encourage their adoption (Frois et al., 2016). Under current FDA guidelines, a biosimilar will be referenced to the name of the innovator biopharmaceutical plus a differentiating suffix (e.g., *filgrastim-sndz*), which may lead to confusion among prescribers and patients. A study by the FTC reports that a drug’s name can have a substantial impact on a patient’s or physician’s acceptance of the substitute (Malkiewicz, 2016).

These high barriers are expected to limit the entry of the number of competitive biosimilars relative to the number of small-molecule generic drugs – following the Hatch-Waxman Act – which have led to decreased costs to patients and health insurance companies (Frois, *et al.*, 2016). This disparity between loss of sales for pharmaceuticals compared to biopharmaceuticals is not unexpected and supported by several important considerations described above. Some analysts are concerned that the lack of an abbreviated approval pathway, inability for the pharmacists to readily substitute the biosimilar for the biologic, and naming convention and regulatory barriers within the states could reduce the likelihood that follow-on biologics are adopted to provide the financial incentive for the development of these new drugs (Frois, *et al.*, 2016; Malkiewicz, 2016; Silber, 2013).
Chapter Three

RESEARCH DESIGN

The Biosimilars Act (BPCIA) is likely to have a substantial impact on innovation in the large and rapidly growing sector of the biopharmaceutical industry. The legislative intent of Congress to enact the BPCIA was to lower biologic drug prices for patients while stimulating biotechnology research and development. Whether the Act will fulfill these objectives is still to be determined.

Research Question

In my dissertation research, I analyze the impact of the BPCIA and its market exclusivity protections on biopharmaceutical innovation. My research design and methodology closely examine how selected indicators of research and development within the biopharmaceutical industry responded to the enactment of the BPCIA.

The question of optimal IP protection to stimulate innovation while preserving public access to inventions has proven to be difficult to study empirically (Cockburn, 2011; Qian, 2007). Researchers have attempted to answer this question using various proxy indicators with numerous data points. From several prior studies, there is no consensus among researchers about the relationship of changing IP protection and the effects on innovation (Aghion, Howitt, & Prantl, 2013; Allred & Park, 2007; Williams, 2015).
The Significance of the Study

Answering my research question – what effect the BPCIA and its exclusivity provisions had on biopharmaceutical innovation – will address the persistent public policy argument of whether stronger exclusivity affects innovation and if so, whether the effects are positive or negative. Having a clear interpretation of empirical data can support or refute this linking, which is important for further IP protection policy analysis as it pertains to encouraging innovation in biopharmaceuticals.

Within this context, the broader purpose of this study is to analyze the optimal level of exclusivity protections in the biopharmaceutical industry to stimulate research and innovation for new drug development. Answering the question whether longer exclusivity encourages biopharmaceutical research and development has important implications for public policy because accessible and effective healthcare is one of the major areas affecting large populations of stakeholders.

Unlike conventional small-molecule drugs, many biologics can target specific molecular processes and effectively treat diseases that until recently had poor prognosis or available treatments could only relieve symptoms. Since 2011, FDA has approved new biologics for the treatment of a wide range of illnesses in addition to various types of cancers, including Lupus, Crohn's disease, rheumatoid arthritis, multiple sclerosis, kidney failure, asthma, diabetes and high cholesterol. It is important to create policies that encourage the development of these promising drugs. However, as these therapies continue to enter the market, their lifesaving power will be limited if costs make them inaccessible to the millions of patients who need them.
Methods

I use published data and compile time-series analyses to identify major shifts in various biopharmaceutical industry metrics of innovation (i.e., indicators) in response to key events (i.e., milestones) associated with the emergence, development and enactment of the BPCIA. The purpose of this analysis is to measure significant changes in indicators that mark increases or decreases in innovation in biopharmaceuticals that may have occurred in response to implementation of the Biosimilars Act. Through this analysis, I answer a broader question “Do changes in market exclusivity protection affect innovation in biopharmaceuticals?”

The indicators are specific data points that I ascribe to be closely associated with innovation activities in the biopharmaceutical industry. I use these indicators to get a broader, more definitive view on changes that might have resulted from the enactment of the BPCIA. For the purpose of my research, I focus on data that pertains to the biopharmaceutical industry.

The raw industry data (i.e., clinical trials and FDA approvals) is assembled into aggregates and the data is compiled and presented in both tabular (Appendices 1 and 2) and graphical formats (Chapter 4). The data corresponding to each of data set was analyzed to determine if any changes in the indicator is a random event or associated with the milestone event. T-tests were applied to determine whether the observed changes in the behavior of each indicator and control in response to the milestones is statistically significant.

Controls are used to isolate those changes to the indicator that can be attributed to the BPCIA and not a generalized phenomenon. I examine the selected indicator against the control of NIH funding, which helps isolate the indicator’s behavior from a broader market change that could be a result of factors other than the BPCIA. The use of controls is necessary to account for
changes in the indicator that may be unrelated to the examined event. Using a control is an important aspect of my research, allowing me to establish a causal relationship between the BPCIA and biopharmaceutical innovation as measured by the resulting change in the data.

I chose this methodological approach for several reasons. The raw data related to the indicators is published and easily sourced from various organizations that collected it over many years. The use of two different indicators provides me with a greater understanding of any observable correlation between the level of biopharmaceutical innovation activity and the Biosimilars Act. The use of controls helps me support the link between the bill’s enactment and the indicator’s behavior.

To support my conclusions, I also rely on the historical record of legislative history. Valuable statements given during testimony by industry leaders, consumer advocacy groups, venture capital representatives, healthcare organizations and other stakeholders provide valuable insights into what competing interests shaped the objectives and provisions of the BPCIA.

There are several challenges to this methodology, which I anticipated and planned to overcome. They include: sourcing data that is comprehensive and not too generalized to allow me the ability to isolate relevant data points from a broader context and compare it to the control indicators; the data must be reliable and include appropriate time periods without chronological gaps; the raw data must be segmented into short enough time intervals to be relevant to this analysis of measuring resultant changes in the data observations.
Three Chronological Milestones

Before the enactment of the BPCIA, two other leading events (milestones) took place. The first milestone was when between 2003 and 2004 the European Union designed legislation to create a statutory pathway for the approval of biosimilars. In 2005, the adopted directive went into force, with the first worldwide biosimilar drug Omnitrope (somatropin) approved in the EU in 2006 (EMA, 2016). In the U.S., the drug was approved by the FDA in 2008, however, it was approved as an NDA under section 505(b)(2) of the FDCA (FDA, 2008).

The second milestone was the legislative negotiations that took place in the U.S. in 2007-2008 to adopt a separate pathway of regulatory FDA approval of biologics. Finally, the U.S. enacted the BPCIA in March 2010 after the legislature passed the bill in late December 2009.

It is likely that these three milestone events (EU legislation, U.S. negotiations and BPCIA enactment) were of fundamental importance to the biopharmaceutical industry because they altered the landscape for new biologic drug development and subsequent regulatory approval, market exclusivity and litigation strategies pertaining to biologics.

Hypotheses:

1) The development and enactment of the biosimilars legislation in Europe in 2004 triggered an increase in biologics R&D investment by the U.S. biopharmaceutical industry in anticipation of similar legislation developing in the U.S.

2) Discussions by U.S. lawmakers in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity in the U.S. in anticipation of an abbreviated pathway for biologics in the U.S.
3) Enactment of the BPCIA in 2010 resulted in increased biopharmaceutical research and development activity in the U.S. in response to the new regulatory pathway and the associated 12-year market exclusivity for biologics.

Clinical Trials Data

Clinical trials as an indicator of innovation activity

Pharmaceuticals must be tested before they are available for use by patients. Drug companies provide the clinical test results to the FDA’s Center for Drug Evaluation and Research (CDER) with evidence to prove the drug is both safe and effective for its intended use. A team of CDER physicians, statisticians, chemists, pharmacologists and other scientists reviews the company's data and proposed labeling. After this independent and unbiased review concludes that a pharmaceutical’s health benefits outweigh its known risks, the drug is approved by the FDA for sale in the U.S. (FDA, August 7, 2017).

Before pharmaceutical companies start clinical trials on a drug, they must conduct extensive preclinical studies. Before clinical trials begin with human subjects, the sponsor performs laboratory and animal experiments to determine what is the biochemical mode of action of the pharmaceutical and whether it is likely to be safe and effective on humans. Then, a series of tests in humans determines if the drug is safe when used to treat a disease and whether it provides a statistically significant health benefit (FDA, August 7, 2017).

Clinical trials are experiments or observations conducted with a limited population of human subjects. These biomedical or behavioral research studies on human participants are
designed to address specific questions about biomedical or behavioral interventions, including novel treatments (e.g., vaccines, pharmaceuticals, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison.

Clinical trials generate data on safety and efficacy. They are conducted only after the sponsors have received the health authority’s and ethics committee’s approvals in the country where marketing and sale of the medication are proposed to be offered to patients. These authorities are responsible for vetting the risk-benefit ratio of the trial – their approval does not mean that the therapy is either safe or effective, only that the clinical trial may be conducted in their jurisdiction.

Depending on the product type and development stage, clinical investigators seek volunteers to join small pilot studies and subsequently conduct progressively larger comparative studies using more people to evaluate the drug. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. The clinical study design strives to evaluate the scientific validity and reproducibility of the results (NIH, January 2017).

Every clinical study is led by a principal investigator, who is often a licensed medical doctor. Clinical studies also have a research team that may include physicians, nurses, statisticians and other allied health professionals.

Clinical studies can be sponsored or funded by pharmaceutical companies, academic medical centers, voluntary groups, and other organizations. Additionally, federal agencies such as the National Institutes of Health, the U.S. Department of Defense and the U.S. Department of Veterans Affairs sponsor and fund clinical research (NIH, January 2017).
Clinical trials are used as a measure of innovation because they indicate the availability of potential future drugs that pharmaceutical companies are trying to research, develop and bring to the market. Each year, the biopharmaceutical industry spends billions of dollars on R&D, and the majority is spent on clinical trials (PhRMA, 2015). Approximately 90% of all clinical trial spending in the United States accounts for the biopharmaceutical industry (Getz, 2010).

Trials can be quite costly, depending on a number of factors. In 2013, the biopharmaceutical industry spent almost $10 billion directly on clinical trials. This figure does not include the monies spent by contractors or vendors of the biopharmaceutical companies (Horowitz, 2015). In 2012, about 70% of the potential new medicines in the R&D developmental pipeline represented novel approaches to treating several common and debilitating diseases such as cancer, neurological disorders and diabetes (PhRMA, 2012).

In 2005, when U.S. Senate Committee on Health, Education, Labor, and Pensions held a hearing on FDA’s drug approval process, Executive Director of the National Patient Advocate Foundation, Dr. Nancy Davenport-Ennis, in her testimony said: “Any mandate for larger and longer clinical trials would dramatically increase the overall cost of research and development. Such increases could have a chilling effect on the pace of scientific discovery. Fortunately, the continued development of new, scientifically based capacities to enable shorter, smaller, and smarter clinical trials holds great promise for dramatically reducing the skyrocketing costs associated with the clinical trials component of research and development. Since the cost of conducting a clinical trial sometimes prevents companies from pursuing promising new products (particularly those that would be used only in certain patient sub-populations), any technological advancements that reduce the cost of clinical trials could provide a heretofore lacking economic incentive to expand the scope and scale of the research and development pipeline to include new
products for diseases and conditions that would otherwise be considered too great of a financial risk” (Senate Hearing 109-67, 2005).

**Clinical trials data bank**

Clinical trials involve human subjects and therefore are required to be registered with the FDA. Registration is required for trials that meet the Food and Drug Administration Amendments Act (FDAAA) 801 definition of an Applicable Clinical Trial (ACT) and that were either initiated after September 27, 2007, or on or before that date and were still ongoing as of December 26, 2007. Trials that were ongoing as of September 27, 2007, and reached the Completion Date before December 26, 2007, are excluded.

Applicable Clinical Trials include the following:

- Trials of drugs and biologics: controlled clinical investigations, other than phase 1 clinical investigations, of drugs or biological products subject to Food and Drug Administration (FDA) regulation.

Applicable Clinical Trials generally include interventional studies of FDA-regulated drugs, biological products that meet one of the following conditions (FDA, June 2017):

- The trial has one or more clinical sites in the United States
- The trial is conducted under an FDA investigational new drug application (NDA) or investigational device exemption
- The trial involves a drug, biologic, or device that is manufactured in the United States or its territories and is exported for research.
The FDA makes this data available to the public in a searchable database, which is accessible at www.clinicaltrials.gov. I queried the databank for clinical trials to aggregate the data as described below.

**Search parameters**

The databank of clinical trials available through www.clinicaltrials.gov is searchable by a variety of parameters. Many of these search criteria pertain to the trial process (e.g., information about test subjects, health conditions, geographical location of the trial). For my data collection process and research, I did not utilize these additional filters because the specific data components are not relevant to my measuring biopharmaceutical innovation levels.

The search filters that I utilized were: *Interventions, Phase, Funder Type* and *Date First Received*.

An intervention search specifies a process or action that is the focus of the clinical trial. Per the FDA Clinical Trials databank search engine, these can be drugs, biologics, medical devices, procedures or other products that are either investigational or already available. A combination of two or more intervention types can be used in one study (e.g., drug and biologic or drug, biologic and device).

For the purpose of my research, I used the term “biological” in the intervention filter to extract all clinical trials that listed and used a biologic product in the clinical study. For extracting clinical trials on small-molecule drugs, I used the term “drug” as an intervention method.
Five phases of clinical trials

Clinical trials of new drugs or biologics are commonly classified into five phases. Each phase is treated and recorded in the www.clinicaltrials.gov databank as a separate clinical trial. The testing process of a new pharmaceutical agent normally proceeds through four phases: 0, 1, 2 and 3. If the new drug successfully passes through these four phases, it is eventually approved by the FDA for sale and use in the general population. Phase 4 includes clinical trials after the drug is approved for sale by the FDA.

Each of the five clinical trial phases has a specific purpose and helps investigators answer different questions to evaluate the proposed pharmaceutical.

Phase 0 clinical trials are the “first-in-human trials” when a single subtherapeutic dose of the drug is administered to a small number of test subjects (usually 10 to 15 people). In this phase, scientists gather preliminary data on pharmacodynamics (i.e., what the drug does in the body) and pharmacokinetics (i.e., what the body does to the drugs). Phase 0 clinical trials collect data on absorption, distribution, metabolism, interaction and excretion of the drug to verify that these metabolic and biochemical processes occur as predicted.

Phase 1 clinical trials test the new agent on a small group of human test subjects (usually 20-80 people) with the objective to evaluate the safety, determine safe dosage and begin to identify any side effects (NIH, June 2017). Because side effects can be mild or undetectable in the short term, or they may affect only a few subjects, phase 1 trials are not exhaustive nor expected to determine all possible side effects. This phase typically lasts for several months (FDA, May 2017).
Phase 2 clinical trial testing is conducted on a larger group of subjects (usually 100-300 people) to determine the efficacy of the drug (i.e., presence or absence of a therapeutic effect in the body) and to further evaluate its safety (NIH, June 2017). Since the size of the test group is larger, researchers attempt to identify the less common side effects. Phase 2 clinical trials typically last from several months to 2 years (FDA, May 2017).

Phase 3 clinical trial testing involves larger groups of people (usually 1,000–3,000 people) and is aimed at confirming the drug’s efficacy (i.e., capacity to yield a therapeutic effect in the body), evaluating its effectiveness (i.e., how significant the therapeutic effect is), monitoring side effects, comparing it to commonly used treatments and collecting other information for the medication to be deemed safe in humans (NIH, June 2017). Phase 3 clinical trials take 1 to 4 years (FDA, May 2017).

Phase 4 clinical trials are post-marketing studies conducted when the drug is already approved for sale and is used in patients in the general population. These studies collect and report additional information, such as risks, benefits, optimal use and effects within certain subgroups of patients (NIH, June 2017). Phase 4 trials are ongoing and are particularly relevant when side effects from the medication require time to become evident.

Phases 2 and 3 clinical trials as indicators of innovation

For the purpose of my research to measure biopharmaceutical innovation, I collected clinical trials in phase 2 and phase 3 and did not include data for studies in phases 0, 1 and 4.
While most drugs are tested and evaluated in clinical trial phases 0 and 1, and the FDA panel reviews their results, these trials are not required to be submitted to the clinical trials databank. The U.S. Congress, in 2007, signed into law a bill which requires phase 2 and phase 3 clinical trials to be registered by the sponsor on the clinical trials website compiled by the National Institutes of Health. Some phase 0 and phase 1 clinical trials are available through the databank, but this data is not complete and therefore cannot be used as a reliable indicator of innovation.

Phase 4 trials were not included in my data because they are continuous post-approval studies for pharmaceuticals already on the market, and therefore these trials are also not valid indicators of innovation.

Compared to phase 1, phase 2 clinical trials are costlier, involve more patients and take more time (2 years compared to several months). Therefore, sponsors must have a commensurate level of confidence in commercial success (i.e., therapeutic effectiveness and existence of sufficient patient market for the product being developed). The number of clinical trials for phase 2 may, therefore, be considered a more sensitive indicator of innovation activity in biopharmaceuticals than any other phase.

The reported numbers of clinical trials do not equal the number of biologics tested because each drug generates multiple trials at different test sites that generate their own record. Clinical trials are an indicator of the overall research and innovation activity in biopharmaceuticals, and the overall trend can be observed.
**Funder types**

Clinical trials may be funded by a pharmaceutical, biotechnology, medical device company or a governmental organization. Certain functions necessary for clinical trials, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory.

In the clinicaltrials.gov databank, the funder type describes the organization that provides funding or support, such as facilities and scientific expertise. Organizations listed by the FDA as sponsors and collaborators for a study are considered the funders of the study.

There are four types of funders (NIH, June 2017):

- Industry
- National Institutes of Health (NIH)
- Other U.S. Federal agency (e.g., FDA, CDC, U.S. Department of Veterans Affairs)
- All others (e.g., universities, research intuitions, organizations, individuals)

In my data analysis, clinical trials funded by the industry are labeled as Indicator 1, while clinical trials funded by research institutions – as Indicator 2.

**NIH and Federal funders as a control**

As a Control 1, I used clinical trials data by NIH and federal funders (combined together). The NIH and other federal agencies have a fixed annual budget set by Congress and
therefore are less responsive to changes in technology, regulatory incentives or legislative policies targeting innovation. While the NIH provides significant financial grants for research to institutions and funds the vast majority of basic drug discovery research, it also conducts its own clinical trials for late-stage drug discovery. However, unlike industry, NIH generally does not commercialize its pharmaceutical and biopharmaceutical discoveries, it rather lets industry and research institutions to lead the field of the new drug development by providing them funding for basic research (Sampat & Lichtenberg, 2011).

Although the total NIH budget has declined somewhat from 2010, and the sequestration in 2013 has further lowered its budget, the funds spent on intramural research (i.e., research conducted within the NIH) has remained relatively steady. The NIH lowered its extramural research funding (i.e., research conducted by outside organizations) in response to the budget cuts (BRIMR, 2014). Therefore, the NIH’s own innovation research was not affected by the reduced budget, and the clinical trials conducted by the NIH can act as a reliable control against industry and institutionally funded clinical trials data.

*Time Frame for Clinical Trials Data*

The time period chosen for analysis starts in 2002 when the European Union began to discuss implementing a new regime for approving biologics. Because the U.S. biopharmaceutical industry was looking to Europe for signs of reforms to be implemented by the U.S., I surmised that fluctuations in my indicators would be observed during or following this time period. In the United States, negotiations were underway on Capitol Hill starting in 2007. These discussions culminated in the passage of the BPCIA on December 24, 2009. The law was signed into effect
on March 10, 2010. Therefore, I expected to observe further changes in applications for clinical trials coinciding with this period.

**FDA Approvals Data**

*FDA Drug Approvals as an Indicator of Innovation Activity*

The entry of new drugs and biological products as new treatments for various conditions and diseases is often an outcome of innovation activity that originated on the lab bench. Each year, a number of new drugs and biological products is approved by the FDA, some of which are innovative products never before available for patients, and some are the same as (i.e., generics), or related to, previously approved products.

The Federal Drug Administration is the governmental body with jurisdiction over testing and approving pharmaceuticals for consumption by humans. In the United States, all clinical trials submitted to the FDA as part of the drug approval process are independently assessed by clinical experts within the Food and Drug Administration, including inspections of primary data collection at selected clinical trial sites (FDA, August 18, 2015).

The mission of FDA’s Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. CDER does not test drugs, although the Center's Office of Testing and Research does conduct limited research in the areas of drug quality, safety, and effectiveness (FDA, July 7, 2015).
Data Source for FDA Approvals

The FDA makes available for public a searchable databank of approvals given to new small-molecule and biologic drugs. This Drugs@FDA data bank is accessible through the FDA’s website and is searchable by month, year, approvals for original products, generics approvals, supplemental approval and tentative approvals.

Categories of FDA Approvals: BLA, NDA and ANDA

For the purposes of FDA review and approval, new drugs are classified as new molecular entities (NME). Many of these products contain active moieties that have not been previously approved by the FDA, either as a single-ingredient pharmaceutical or as part of a combination product. However, some of these NME drugs are so characterized even though they contain active moieties that are closely related to those in previously approved molecular entities. For example, CDER classifies biological products submitted in an application under Section 351(a) of the PHSA as NME, regardless of whether a related active moiety has been previously approved in a different product by the Agency. FDA’s NME classification of a drug is distinct from the determination of whether a drug product is a new chemical entity (NCE) (FDA, August 17, 2017).

In the searchable databank of FDA approvals, new molecular entities have two distinct types of application: new drug application (NDA) and biologic license application (BLA), used for small-molecule drugs and biologics, respectively.
For my research, I collected and sorted data for both BLA and NDA approvals. In my data analysis, BLA approvals are labeled as Indicator 3, while NDA approvals – as Control 2.

The third application type – abbreviated new drug application (ANDA) – is for generic small-molecule drugs. It is the most numerous type of FDA approvals and therefore they are not suitable for measuring innovation in biopharmaceuticals. Nevertheless, during data collection, I generated and sorted this data to see if there were notable changes in generic approvals during the time period that is significant for the analyses of data pertaining to novel biologic and small-molecule drugs.

Additional Classifications of FDA Approvals

The NDA approvals belong to one of the two review types: standard or priority. Priority review designation is assigned to applications for drugs that target serious conditions and provide significant improvements in the safety or effectiveness of their treatment, diagnosis or prevention compared to available therapies. Standard review designation is assigned the NDA applications for drugs that do not meet the priority designation criteria (MAPP, 2013). BLA applications for biologics and ANDA applications for small-molecule generic drugs do not have these designations assigned to them.

Another classification, also assigned only to NDA applications, is the submission classification type.
There are several submission classification types, as follows (MAPP, 2015):

Type 1 – new molecular entity;

Type 2 – new active ingredient;

Type 3 – new dosage form;

Type 4 – new combination;

Type 5 – new formulation or other differences;

Type 6 – new indication or claim, the same applicant (this type is no longer used);

Type 7 – previously marketed but without an approved NDA;

Type 8 – a prescription to over-the-counter status;

Type 9 – a new indication or claim, drug not to be marketed under this type after approval;

Type 10 – a new indication or claim, drug not to be marketed under this type after approval;

Type 1/4 – type 1 (new molecular entity) and type 4 (new combination);

Type 2/3 – type 2 (new active ingredient) and type 3 (new dosage form);

Type 2/4 – type 2 (new active ingredient) and type 4 (new combination);

Type 3/4 – type 3 (new dosage form) and type 4 (new combination)

During the sorting of FDA approvals data for NDA applications, I excluded from my analysis types 3, 6, 7, 8, 9 and 10, because these approval types do not result from innovation and novel research activity.
**Timeframe for FDA Approvals Data**

The time period chosen for analysis of FDA approvals is 2003 to 2016. This time frame lags the 2002-2016 timeframe of clinical trials data by one year because granting of FDA approval is the final step before the drug is ready to be marketed to the public.
Chapter Four

RESULTS

Clinical Trials Data

![Graph showing the number of biologics clinical trials funded by the biopharmaceutical industry from 2002 to 2016]

**Figure 1.** Industry-funded clinical trials of biologics for phase 2 and 3 combined (Table 4)

The number of clinical trials funded by the biopharmaceutical industry (Indicator 1) for phase 2 and phase 3 combined is plotted for the years 2002 through 2016. The combined phase 2 and 3 number of industry-sponsored clinical trials increased significantly in 2005 by 541% from 49 to 314.

The second significant increase in the number of trials is observed in 2008 when the combined number of phase 2 and phase 3 trials increased by 29% from 366 to 473. This was followed by a period of fluctuation between 2010 and 2013. Since the peak in 2009, the combined phase 2 and phase 3 clinical trials remained relatively flat through 2016.

The linear trendline for clinical trials by biopharmaceutical companies shows a 25% average annual increase during the 15 years plotted on the graph. Statistical analyses for Indicator 1 are presented in Appendix 4.
Figure 2. Industry-funded clinical trials of biologics for phases 2 and 3 (Table 4)

The numbers of phase 2 and phase 3 clinical trials funded by the biopharmaceutical industry (Indicator 1) for the years 2002 through 2016 are plotted separately. A significant increase in the number of trials is observed in 2005: the number of phase 2 trials increased by 558% from 24 to 158, while phase 3 trials increased by 524% from 25 to 156.

The second significant increase in the number of trials is observed in 2008. The number of phase 2 trials increased by 46% from 195 to 285, while phase 3 increased slightly from 171 to 188. This was followed by a period of fluctuation for phase 2 trials between 2010 and 2013.

Since the peak of 2005, phase 3 clinical trials remained relatively flat through 2016.
The numbers of industry-funded clinical trials (Indicator 1) in phase 2 and phase 3 are plotted for the years 2002 and 2016 as percentages relative to each other. During this period, the ratio of phase 2 and phase 3 trials fluctuated. Phase 2 trials constituted between 49% and 68% with an average of 58%, while phase 3 trials ranged between 32% and 51% for an average of 42%.

Between 2002-2003, the ratio of phase 2 to phase 3 is approximately 2:1. In 2004, the ratio approached 1:1 and remained relatively constant till 2007. In 2008, the ratio reverted to 3:2.
The number of clinical trials funded by federal government (Control 1) for phase 2 and phase 3 combined is plotted for the years 2002 through 2016. The number of phase 2 and phase 3 trials increased in 2005 by 69% from 98 to 166. This is followed by a sustained decrease in the number of phase 2 and 3 clinical trials between 2006 and 2012 with an overall decrease of 65% from 170 to 60 clinical trials.

From 2012 to 2015, the combined phase 2 and 3 federally funded clinical trials experienced an increase by 73% from 60 to 104.

The linear trendline for federally funded clinical trials shows an overall 2% average annual decrease during the 15 years plotted on the graph. Statistical analyses for Control 1 are presented in Appendix 5.
The numbers of phase 2 and phase 3 clinical trials funded by the federal government (Control 1) are plotted separately for the years 2002 through 2016. The number of phase 2 trials in 2005 increased by 69% from 88 to 149, while phase 3 trials increased by 70% from 10 to 17.

The number of phase 2 clinical trials gradually decreased during 2006-2012 by 70% from 154 to 54, and then gradually increased during 2012-2016 by 57% from 54 to 85.

The number of phase 3 clinical trials averaged 13 per year for the 15 years between 2002 and 2016. The largest annual decrease of 41% was in 2008 (from 22 to 13). The largest annual increase of 133% was in 2013 (from 6 to 14).
Figure 6. Federally funded clinical trials of biologics: phases 2 and 3 percentages (Table 3).

The numbers of federally funded clinical trials (Control 1) in phase 2 and phase 3 are plotted as percentages relative to each other between the years 2002 and 2016. During this period, the ratio of phase and phase 3 trials was relatively constant. Phase 2 trials constituted between 83% to 91% with an average of 88%, while phase 3 trials ranged between 9% to 17% for an average of 12%.
Figure 7. Industry-funded and federally funded phase 2 and 3 clinical trials for biologics (Table 3 and Table 4)

The numbers of clinical trials funded by the biopharmaceutical industry (Indicator 1) for combined phase 2 and phase 3 are plotted side-by-side with federally funded clinical trials (Control 1) for the years 2002 through 2016. From 2002 to 2004, the number of federally funded phase 2 and 3 clinical trials was higher than the number of industry-funded trials. From 2005, the number of federally funded clinical trials increased, however, the corresponding number for industry-funded trials increased substantially, outpacing the number of federally funded trials significantly each year through 2016.
Figure 8. Industry-funded phase 2 and 3 clinical trials as a percentage of federally funded clinical trials for biologics (Table 3 and Table 4)

The number of clinical trials funded by the biopharmaceutical industry (Indicator 1) for combined phase 2 and phase 3 is plotted as a percentage of federally funded clinical trials (Control 1) for the years 2002 through 2016. From 2002 to 2004, the percentage of industry-funded clinical trials ranged between 41% and 50%. In 2005, that percentage increased to 189% and continued to increase in the following two years to 200% and 242%.

In 2008, the percentage again significantly increased to 434% and continued above the trendline for the next two years. The next significant increase was in 2011 (596%) and further increased to 622% in 2012. These years of increase of industry-funded clinical trials relative to federally funded clinical trials were followed by a decrease ranging from 396% and 490% for the years 2013 to 2016.

The linear trendline for clinical trials funded by the biopharmaceutical companies for combined phase 2 and phase 3 as a percentage of federally funded clinical trials shows a 35% average annual increase during the 15 years plotted.
The number of clinical trials funded by institutional sponsors (Indicator 2) for phase 2 and phase 3 combined is plotted for the years 2002 through 2016. A significant increase in the number of trials is observed in 2005 when the number of phase 2 and phase 3 clinical trials increased by 439% from 18 to 97.

The second significant increase in the number of trials is observed in 2008 when the number of phase 2 and phase 3 trials increased by 40% from 111 to 155.

The combined number of phase 2 and 3 clinical trials gradually increased between 2013 and 2016: from 161 to 205 in 2014 (27%), to 236 in 2015 (15%), to 264 in 2016 (12%).

The linear trendline for clinical trials by institutional sponsors shows a 16% average annual increase during the 15 years plotted on the graph.

Statistical analyses for Indicator 2 are presented in Appendix 6.
Figure 10. Institutionally funded clinical trials of biologics for phases 2 and 3 (Table 5)

The numbers of phase 2 and phase 3 clinical trials funded by the institutional sponsors (Indicator 2) are plotted side-by-side for the years 2002 through 2016. A significant increase in the number of trials in both phases is observed in 2005: the number of phase 2 trials increased by 500% from 13 to 78, while phase 3 increased by 280% from 5 to 19. In 2006, phase 3 trials further increased by 58% from 19 to 30.

The second significant increase in the number of trials is observed in the period from 2006 to 2009. The number of phase 2 trials increased by 113% from 61 to 130.

Since 2006, phase 3 clinical trials fluctuated within a moderate range between 25 and 30 clinical trials. However, in 2011, phase 3 clinical trials increased by 80% from 25 to 45 trials.

From 2013 to 2016, phase 2 trials experienced a sustained increase: from 128 to 169 in 2014 (32%), to 184 in 2015 (9%), to 225 in 2016 (22%).
The numbers of institutionally funded clinical trials (Indicator 2) in phase 2 and phase 3 are plotted as percentages relative to each other between the years 2002 and 2016. During this period, the ratio of phase and phase 3 trials varied slightly. Phase 2 trials constituted between 61% to 85% with an average of 76%, while phase 3 trials ranged between 15% to 39% for an average of 25%.

During 2002-2003, the ratio of phase 2 to phase 3 is approximately 3:2. In 2004, the ratio diverged to 3:1 and remained relatively constant till 2007. In 2008, the ratio approached 4:1.
Figure 12. Institutionally funded and federally funded phase 2 and 3 clinical trials for biologics (Table 3 and Table 5)

The numbers of clinical trials funded by research institutions (Indicator 2) for combined phase 2 and phase 3 are plotted side-by-side with federally funded clinical trials (Control 1) for the years 2002 through 2016. From 2002 to 2007, the number of federally funded phase 2 and 3 clinical trials was higher than the number of institutionally funded trials. From 2008, the number of federally funded clinical trials decreased, while the corresponding number for institutions increased and began to outpace the number of federally funded trials.
The number of clinical trials funded by research institutions (Indicator 2) for combined phase 2 and phase 3 is plotted as a percentage of federally funded clinical trials (Control 1) for the years 2002 through 2016. From 2002 to 2004, the percentage of institutionally funded clinical trials decreased from 32% in 2002 to 18% in 2004. In 2005, that percentage increased to 58%, and in 2007 it increased to 74%.

In 2008, the percentage of institutionally funded clinical trials significantly increased to 142% (outpacing federally funded trials) and continued on an upward trajectory peaking in 2012 at 280%, almost doubling the 2008 value. These years of increase of institutionally funded clinical trials relative to federally funded clinical trials were followed by a moderate decrease ranging from 179% to 275% for the years 2013 to 2016.

The linear trendline for clinical trials funded by research institutions for combined phase 2 and phase 3 as a percentage of federally funded clinical trials shows a 20% average annual increase during the 15 years plotted.
Figure 14. Relative proportions of phase 2 and 3 clinical trials funded by industry, research institutions and federal government (Table 3, Table 4 and Table 5)

The numbers of clinical trials of biologics in phase 2 and 3 are plotted as percentages of industry, institutionally and federally funded trials (Indicator 1, Indicator 2 and Control 1, respectively) for the years 2002 through 2016. In 2002-2004, the proportion of industry-funded clinical trials was between 21% and 30%. In 2005, this proportion significantly increased to 54%, which equated to more than half of all clinical trials. In 2011, the proportion of industry-funded phase 2 and 3 clinical trials of biologics peaked at 66% (almost two-thirds of all clinical trials).

From 2002 to 2009, the proportion of institutionally funded clinical trials was relatively constant between 11% and 21%. In 2010, it increased to 24% and continued to increase gradually reaching 35% in 2016. In 2002-2004, the proportion of federally funded clinical trials was between 58% and 65%, comprising the majority of all clinical trials. In 2005, this proportion significantly decreased to 29% and continued to decline, reaching 15% in 2008 and remaining in a low range (between 10% and 17%) for the years plotted.
Figure 15. Annual percent change relative to the previous year for the industry, federally and institutionally funded clinical trials of biologics for phase 2 and 3 combined (Table 3, Table 4 and Table 5)

The annual percent change in the number of phase 2 and 3 clinical trials is plotted for each funder type – industry, research institutions and federal government (Indicator 1, Indicator 2 and Control 1, respectively) – for the period 2003-2016. The percent change is calculated based on the previous year.

For the year 2005, all three funder types experienced an increase, with the industry having the highest increase of 540% compared to 2004. For 2007 and 2008, federally funded clinical trials experienced a decrease of 11% and 28%, respectively. During the same two years, industry- and institutionally funded clinical trials increased. In 2009, all three funding sources increased their clinical trials with the federally funded trials having the greatest annual increase of 23%. In 2010, all three groups of clinical trials decreased.
FDA Approvals Data

![FDA Approvals Chart](image)

**Figure 16.** FDA approvals of BLAs for 2003-2016 (Table 6)

The number of FDA approvals for biologic license applications (BLA) (Indicator 3) is plotted for the years 2003 through 2016. Between 2003 and 2008, the average number of approvals was 3 per year. In 2009, approvals more than doubled to 7 for three consecutive years. The average number of approved BLA applications between 2009 and 2013 was 6.2 per year. Between 2014 and 2016, the average number was 12.3.

The linear trendline for the number of FDA approvals of biologic license applications shows a 0.8 average annual increase of approvals during the 14 years plotted on the graph. This represents a 13% average annual increase (as derived from the average of 6.4 approvals per year).

Statistical analyses for Indicator 3 are presented in Appendix 7.
The number of FDA approvals for new drug applications (NDA) (Control 2) is plotted for the years 2003 through 2016. For most years, the number of NDA approvals ranged from 43 and 57 per year. In 2007 and 2009, the annual approvals decreased to 35 and 37, respectively. In 2014 and 2015, the number of approvals increased to 71 and 78, respectively, before decreasing to 57 in 2016.

The linear trendline for the number of FDA approvals of NDAs shows a 2.1 average annual increase of approvals during the 14 years plotted on the graph. This represents a 4% average annual increase (as derived from the average of 51.6 approvals per year).

Statistical analyses for Control 2 are presented in Appendix 8.
The number of FDA approvals for biologic license applications (BLA) is plotted for the years 2003-2016 as a proportion the total number of new drug approvals (both BLA and NDA). Between 2003 and 2008, the average proportion of BLAs was 7% per year. In 2009, the annual percentage of BLA approvals more than doubled to 16%. The 2010-2013 percentage was declining for four years reaching 7% in 2013. In 2014, the annual percentage of BLA approvals more than doubled again to 13% and continued to increase to 15% in 2015 and 17% in 2016.

The linear trendline for the percentage proportion of FDA approvals for biologic license applications shows a 0.8% average annual increase of approvals during the 14 years plotted.
Chapter Five

DISCUSSION

Milestones and Indicators

As discussed in the Research Design chapter, this research examines three milestone events: Milestone 1 – EU biosimilars legislation in 2004, Milestone 2 – U.S. legislative negotiations in 2007-2008 and Milestone 3 – BPCIA enactment in 2010. These three milestones are analyzed in the context of three hypotheses regarding the effect of each on innovation in biopharmaceuticals.

My data analysis intersects the three milestones with three indicators, where Indicator 1 is the number of industry-funded clinical trials, Indicator 2 is the number of institutionally funded clinical trials and Indicator 3 is the number of FDA approvals of BLAs. Analyzing the trends and changes in these three indicators in response to each of the three milestones helps an observer to understand whether the new regulatory landscape of the BPCIA and the associated events impacted innovation in the biopharmaceutical industry in the United States.

In addition to three indicators, two controls – the number of federally funded clinical trials (Control 1) and the number of FDA approvals of NDA applications (Control 2) – are used to control for analysis of the effect of independent variables (i.e., Milestones 1, 2 and 3) on the dependent variables (i.e., Indicators 1, 2 and 3).
Milestone 1:

Europe Enacts an Abbreviated Pathway for Biologics in 2004

*Hypothesis 1:* the development and enactment of the biosimilars legislation in Europe in 2004 triggered an increase in biologics R&D investment by the U.S. biopharmaceutical companies and research institutions in anticipation of similar legislation developing in the U.S.

Data analyses

To determine if the U.S. biopharmaceutical industry responded to the enactment of the EU legislation (Milestone 1), the numbers of U.S. clinical trials for biologics (Indicators 1 and 2) were measured and analyzed.

*Milestone 1 – Indicator 1: Industry-Funded Clinical Trials of Biologics*

The annual number of phase 2 and 3 clinical trials of biologics funded by biopharmaceutical companies (Indicator 1) increased in 2005 by 541% from 49 to 314 (Figure 1). The significant increase in 2005 is observed for the number of trials in both phases: phase 2 trials increased by 558% from 24 to 158, phase 3 trials increased by 524% from 25 to 156 (Figure 2).

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 1 (Appendix 4) shows that industry-sponsored clinical trials increased from an average of 39 to 340 per year. This increase is statistically significant (P-Value = 0.000).
The ratio of phase 2 to phase 3 industry-funded clinical trials was approximately 2:1 during 2002-2003 (Figure 3). In 2004, the ratio approached 1:1 and remained relatively constant till 2007 (Figure 3). This observation points to the fact that more potential biologic drugs began to be tested in the earlier phase (i.e. Phase 2).

Comparing the numbers of industry-funded clinical trials to the corresponding numbers of federally funded clinical trials (Control 1 – NIH and other federal agencies), in 2005, phase 2 and 3 trials of biologics showed a comparatively modest increase of 69% from 98 to 166 (Figure 4). Observing each phase separately for 2005, phase 2 trials increased by 69% from 88 to 149, while phase 3 trials increased by 70% from 10 to 17 (Figure 5).

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Control 1 (Appendix 5) shows that federally sponsored clinical trials increased from an average of 95 to 162 per year. This increase is statistically significant (P-Value = 0.007).

While the annual number of federally funded phase 2 and 3 clinical trials increased by 69% in 2005, the corresponding number for industry (Indicator 1) increased substantially more by 541%, which is 7.8 times higher. From 2002 to 2004, the numbers of phase 2 and 3 clinical trials funded by the biopharmaceutical companies trailed the federally funded clinical trials. The year 2005 marked the first year when industry-funded phase 2 and 3 clinical trials of biologics exceeded the number of federally funded trials and continued to outpace them for all following years (Figure 7).

The number of industry-funded clinical trials expressed as a percentage of federally funded clinical trials ranged between 41% and 50% from 2002 to 2004. In 2005, that percentage
increased to 189% and continued to increase in the following two years to 200% in 2006 and 242% in 2007 (Figure 8).

The timing of absolute increases (i.e., without reference to a control) in the number of phase 2 and phase 3 industry-funded clinical trials (Indicator 1), as well as relative increases compared to Control 1 (i.e., federally funded clinical trials), coincides with the European Union enacting legislation for the approval of biosimilars in 2004 (Milestone 1). This data supports the hypothesis that the U.S. biopharmaceutical industry responded favorably to the EU legislation by increasing investment in research and development of biologic agents (as measured by the number of phase 2 and phase 3 clinical trials) in anticipation of similar legislation developing in the U.S.

*Milestone 1 – Indicator 2: Institutionally Funded Clinical Trials of Biologics*

The combined number of phase 2 and 3 clinical trials of biologics funded by research institutions (Indicator 2) increased by 439% in 2005 from 18 to 97 (Figure 9). A significant increase in the number of trials for both phases is observed in 2005: phase 2 trials increased by 500% from 13 to 78, phase 3 trials increased by 280% from 5 to 19 (Figure 10). Phase 3 trials further increased in 2006 by 58% from 19 to 30, constituting a two-year increase of 500% (Figure 10).

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 2 (Appendix 6) shows that institutionally sponsored clinical trials increased from an average of 22 to 100 per year. This increase is statistically significant (P-Value = 0.000).
These increases in numbers of institutionally funded clinical trials are considerably higher than the corresponding growth in federally funded clinical trials (Control 1 – NIH and other federal agencies). The number of federally sponsored phase 2 trials increased in 2005 by 69% from 88 to 149, and phase 3 trials increased by 70% from 10 to 17 (Figure 5); the combined number of federally sponsored trials in phase 2 and 3 increased by an overall 69% in 2005 from 98 to 166 (Figure 4).

The absolute number of federally funded phase 2 and 3 clinical trials (Control 1) remained higher than the number of institutionally funded trials from 2002 to 2007 (Figure 12).

Analyzing the number of clinical trials funded by research institutions (Indicator 2) for combined phase 2 and phase 3 as a percentage of federally funded clinical trials (Control 1), shows that from 2002 to 2004, the percentage of institutionally funded clinical trials decreased from 32% in 2002 to 18% in 2004 (Figure 13). However, in 2005, that percentage value increased to 58%; in 2007, it further increased to 74% (Figure 13).

The timing of absolute increases in the number of phase 2 and phase 3 institutionally funded clinical trials (Indicator 2), as well as relative increases compared to federally funded clinical trials (Control 1), follows EU enacting legislation for the approval of biosimilars in 2004 (Milestone 1). This observation supports the hypothesis that U.S. research institutions responded favorably to the European legislation by increasing research activities for biologics in anticipation of similar legislation developing in the U.S. This increased response by research institutions in the number of phase 2 and phase 3 clinical trials is similar to the response by biopharmaceutical companies.
Milestone 1 – Indicators 1 vs. 2 vs. Control

Figure 14 plots the relative proportions of phase 2 and 3 clinical trials funded by industry, research institutions and federal government (Table 3, Table 4 and Table 5).

The proportion of industry-funded clinical trials (derived from Indicator 1) from 2002 to 2004 was between 21% and 30%; however, it increased significantly to 54% in 2005, which equated to more than half of all clinical trials. The proportion of institutionally funded clinical trials (derived from Indicator 2) from 2002 to 2004 declined from 18% to 11%, but it returned to 17% in 2005 and remained within this range until 2007. Therefore, no significant change in the percent proportion of institutionally funded clinical trials was observed following the enactment of the EU’s biologics legislation in 2004.

The proportion of federally funded clinical trials (derived from Control 1) from 2002 to 2004 was between 58% and 65%, comprising the majority of all clinical trials. This percentage significantly decreased in 2005 to 29% and continued its decline to 24% in 2007. Despite the increase in the absolute number of federally funded clinical trials, their proportion relative to the total number of all trials across the three funder types decreased because industry-funded clinical trials increased significantly in 2005 in both absolute and relative amounts (by 541% from 49 to 314).

Figure 15 plots the annual percent change relative to the previous year for the industry, federally and institutionally funded clinical trials of biologics for phase 2 and 3 combined to compare the relative magnitude of the response of the Indicators to the 2004 enactment of the EU legislation (Milestone 1). All three funder type groups experienced an increase in 2005. The magnitude of change in the 2005 number of clinical trials was greatest for industry-funded clinical trials (Indicator 1) with 541% annual increase. Federally funded clinical trials (Control 1)
increased by a relatively low 69% in 2005, further decreasing to 2% in 2006 and showing a negative growth of –11% in 2007.

A possible reason why U.S. biopharmaceutical companies showed the greatest reaction to the Milestone 1 may have been the expectation that they would benefit from the adoption of the U.S biologics legislation similar to the EU framework. As the stakeholder with the greatest potential to capitalize on the policy shift, it is expected that the industry’s investments into biopharmaceutical research and development would show the greatest change.

*Milestone 1 – Indicator 3: FDA Approvals of BLAs*

To determine if the U.S. biopharmaceutical industry responded to the enactment of EU biologics legislation (Milestone 1), the numbers of FDA approvals for biologics (Indicator 3) were measured and analyzed.

FDA approvals lag the commencement of clinical trials by an average of 4.5-6.5 years. Therefore, the measurable responses in Indicator 3 and Control 2 to milestone events would be expected to be delayed by this time frame.

The average number of BLA approvals (Indicator 3) between 2003 and 2008 was 3 per year (Figure 16). This number more than doubled in 2009 to 7 and remained there for three consecutive years. This increase occurred 5 years following Milestone 1 of 2004 and it corresponds with the expected time lag.
T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 3 (Appendix 7) shows that FDA approvals of BLAs increased from an average of 3 to 6.8 per year. This increase is statistically significant (P-Value = 0.000).

The number of new drug application (NDA) approvals (Control 2) ranged from 35 to 47 per year between 2005 and 2010 and there was no observable change within 5-6 years following Milestone 1 (Figure 17). T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Control 2 (Appendix 8) shows that FDA approvals of NDAs increased from an average of 44.8 to 47.5 per year. This increase is not statistically significant (P-Value = 0.562).

The numbers of FDA approvals for biologic license applications (BLA) were plotted as a proportion of the total number of all new drug approvals (both BLA and NDA) (Figure 18). Between 2003 and 2008, the average proportion of BLAs was 7% per year; however, in 2009 it more than doubled to 16%. This increase occurred 5 years following Milestone 1 of 2004 and corresponds with the expected time lag. From 2010 to 2013, the BLA proportion was gradually declining for 4 years while still remaining above the 2003-2008 average.

The timing of absolute increases in the number of BLA approvals (Indicator 3), as well as relative increases compared to NDA approvals (Control 2), five years after enacting legislation for the approval of biosimilars in 2004 by the European Union (Milestone 1). Measuring the number of BLA approvals five years after the milestone event, the data supports Hypothesis 1 that the U.S. biopharmaceutical industry responded favorably to the EU legislation by increasing investment in research and development of biologics in anticipation of similar legislation developing in the U.S.
Milestone 1 Conclusions

The announced legislative and policy intent of the European biosimilars legislation was to stimulate innovation and increase access to new biologic therapies in Europe. European drug regulatory body has now assumed the role of encouraging innovation in research and production process of biologics, in addition to its traditional role of evaluating, approving and monitoring the safety of medicines (Milmo, 2014). Specifically, the new EU regulation provided 10-year market exclusivity to new biologic drugs approved by the EMA. This provision was adopted to provide innovator biopharma companies with an incentive to develop new biologic drugs and was welcomed by the biopharmaceutical industry in Europe.

The U.S. industry, which was actively pushing Congress for a regulatory approval pathway, was watching Europe closely as an indication of what was eventually to come to the U.S. approval system (Carver et al., 2010). Patent attorney Ude Lu wrote for Minnesota Journal of Law, Science and Technology: “During 2003 and 2004, patents protecting several multibillion dollar sale biologics expired. Yet innovator companies faced no market competition because, at that time, there was no abbreviated pathway to approve FOBs. Since then, there has been increasing pressure on Congress to provide for an abbreviated approval pathway (i.e., biosimilar pathway, similar to ANDA in the Hatch-Waxman Act to approve FOBs). The pressure on Congress intensified after both the European Union (EU) and Canada implemented their versions of biosimilar pathways in 2004 and 2006 respectively” (Lu, 2014).

However, despite continued pressure on Congress by the industry and the states, things were progressing slowly on Capitol Hill (Carver et al., 2010). Jim Greenwood, President and CEO of the U.S. Biotechnology Industry Organization, speaking at a London press conference in
2005, said: “I think we are probably several years away. There are certainly those in Congress who are advocating a pathway for generics, but there is a fairly widespread understanding in Congress that biologicals are not the same as small-molecules. It is quite a different thing to try to produce a biosimilar. Even tiny variations in structure can stimulate immune responses in patients” (GEN, 2005).

As illustrated by early legislative history, several legislators, including Senator Schumer and Senator Clinton, recognized the need to get a biologics legislation moving forward and hearings in the House and Senate discussing how the U.S. is ought to catch up with Europe where held as early as 2004 and continued into 2006 (Senate Hearing 108-635, 2004; Senate Hearing 109-685, 2006; Senate Hearing 109-850, 2006). Various witnesses representing the industry and trade associations participated in these hearings and stressed the need to actively pursue a comprehensive U.S. biologics legislation. When the President and CEO of the Pharmaceutical Care Management Association Mark Merritt urged Senate Special Committee on Aging to act, he stated the PCMA’s position that “Congress should establish a clear legal pathway to approve biogenerics sooner rather than later.” He pointed to the soaring costs of biologics compared to traditional drugs with no generic alternatives to put the downward pressure on prices, the European Union had already approved legislation for a regulatory pathway for biogenerics (Senate Hearing 109-685, 2006). Jim Guest, President and CEO of Consumers Union, declared that the Union joins others who believe that biogenerics could safely provide savings to patients and that U.S. should follow the European Union in bringing financial relief to consumers (Senate Hearing 109-850, 2006).

Congress listened to these requests and continued to explore the issues surrounding creation of major legislation for biologics. In March of 2007, a Senior Administrator of the
European Commission Pharmaceuticals Unit, Dr. Nicolas Rossignol, was invited to testify before the Senate Committee on Health, Education, Labor, and Pensions. He answered questions by the U.S. legislators, so that they could learn from the European experience, though Senator Schumer cautioned his colleagues consider economic, regulatory and marketplace specifics of the United States (Senate Hearing 110-375, 2007).

The data analyses for Milestone 1 demonstrates that Indicators 1 and 2 (i.e., industry-funded clinical trials and institutionally funded clinical trials, respectively) responded favorably to the EU legislation by increasing the number of clinical trials of biologics in both absolute and relative terms. Indicator 3 (i.e., FDA approvals of Biologic License Applications) also increased five years later. This observation supports the Hypothesis 1 that the development and enactment of the biosimilars legislation in Europe in 2004 triggered an increase in biologics R&D investment by U.S. biopharmaceutical companies and research institutions in anticipation of similar legislation developing in the U.S.

The comparative magnitude of responses by indicators to Milestone 1 was greatest for industry-funded clinical trials (Indicator 1), though institutionally funded trials (Indicator 2) also increased significantly. This may be attributed to the fact that U.S. biopharmaceutical companies may have had the greatest commercial interest in a possibility of biologics legislation emerging in the United States and the potential to capitalize on their investment in biopharmaceutical research and development via the incentives of extended market exclusivity. A study by PricewaterhouseCoopers and the National Venture Capital Association revealed that in 2006 venture capital investing hit a five-year high in the U.S., with $25.5 billion invested. Notably, the life sciences sector was the largest investment sector and accounted for 28% of venture capital money invested (Ware & Littlefield, 2008).
Milestone 2:

The United States Engages in Negotiations Over Biologics Legislations in 2007-2008

_Hypothesis 2:_ the discussions by U.S. lawmakers in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity by U.S. industry and research institutions in anticipation of an abbreviated pathway for biologics in the U.S.

**Data analyses**

To determine if the U.S. biopharmaceutical industry responded to the 2007-2008 policy negotiations over emerging legislation for an abbreviated pathway in the United States (Milestone 2), the numbers of U.S. clinical trials for biologics (Indicators 1, 2 and Control 1) were measured and analyzed.

_Milestone 2 – Indicator 1: Industry-Funded Clinical Trials of Biologics_

The combined number of phase 2 and phase 3 industry-funded clinical trials (Indicator 1) increased by 29% in 2008 from 366 to 473 (Figure 1), which marked the second significant increase in this indicator. This increase was mostly due to an increased number of phase 2 trials which grew by 46% from 195 to 285, while phase 3 trials increased slightly by 10% from 171 to 188 (Figure 2).
T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Indicator 1 (Appendix 4) shows that industry-sponsored clinical trials increased from an average of 340 to 480 per year. This increase is statistically significant (P-Value = 0.006).

By comparison, the combined number of phase 2 and 3 federally funded clinical trials (Control 1) showed a sustained decrease between 2006 and 2012 with an overall decrease of 65% from 170 to 60 clinical trials (Figure 4). For phase 2, the number decreased by 70% from 154 to 54 (Figure 5).

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Control 1 (Appendix 5) shows that federally sponsored clinical trials decreased from an average of 162 to 122 per year. This decrease is statistically significant (P-Value = 0.042).

The number of industry-funded clinical trials (Indicator 1) in phase 2 and 3 in 2008 was 473, while federally funded clinical trials (Control 1) totaled 109 (Figure 7). This year also marked the second major increase in the proportion of industry-funded trials as a percentage of federally funded trials (from 242% to 434%) and the percentage continued to increase above the trendline for the next four years till (Figure 8).

The timing of absolute increases (i.e., without reference to a control) in the number of phase 2 and phase 3 industry-funded clinical trials (Indicator 1), as well as relative increases compared to Control 1 (i.e., federally funded clinical trials), coincides with the 2007-2008 legislative negotiations in the U.S. for developing the new biosimilar policies for the U.S. (Milestone 2). This data supports the hypothesis that discussions by U.S. lawmakers in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity by the U.S. biopharmaceutical companies.
(as measured by the number of phase 2 and phase 3 clinical trials) in anticipation of an abbreviated pathway for biologics in the U.S.

The less pronounced changes in the number of clinical trials for phase 3 may be attributed to the fact that phase 2 clinical trials must be completed successfully before phase 3 trials can commence. On average, only 31% of phase 2 trials are successful and proceed to phase 3 (Mullard, 2016).

*Milestone 2 – Indicator 2: Institutionally Funded Clinical Trials of Biologics*

The number of institutionally funded clinical trials (Indicator 2) increased significantly in 2008 when the combined number of phase 2 and phase 3 trials increased by 40% from 111 to 155 (Figure 9). In the period from 2008 to 2010, the number of phase 2 trials funded by research institutions averaged 122 per year, compared to 74 in 2005-2007; this represents an increase of 66% (Figure 10).

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 2 (Appendix 6) shows that institutionally sponsored clinical trials increased from an average of 100 to 157 per year. This increase is statistically significant (P-Value = 0.005).

By comparison, the number of federally funded clinical trials (Control 1) for phase 2 and 3 decreased between 2006 and 2012 by 65% from 170 to 60 (Figure 4). The number of phase 2 trials decreased by 70% from 154 to 54 in 2012 (Figure 5). The year 2008 marks the first year when the number of institutionally funded clinical trials surpassed that of federally funded trials and continued to outpace it for all following years (Figure 12). The number of institutionally
funded clinical trials expressed as a percentage relative to federally funded trials significantly increased in 2008 to 142% and continued to go up, peaking at 280% in 2012 (Figure 13).

The timing of absolute increases in the number of phase 2 and phase 3 institutionally funded clinical trials (Indicator 2), as well as relative increases compared to Control 1 (i.e., federally funded clinical trials), coincides with the 2007-2008 legislative negotiations in the U.S. for developing the new biosimilar policies for the U.S. (Milestone 2). This data supports the hypothesis that discussions by U.S. lawmakers in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity by U.S. research institutions companies in anticipation of an abbreviated pathway for biologics in the U.S. This increased response by research institutions in the number of phase 2 and phase 3 clinical trials is similar to the response by biopharmaceutical companies.

*Milestone 2 – Indicators 1 vs. 2 vs. Control*

Figure 14 plots the relative proportions of phase 2 and 3 clinical trials funded by industry, research institutions and federal government (Table 3, Table 4 and Table 5). In 2005-2007, the proportion of industry-funded clinical trials (derived from Indicator 1) was between 54% and 58%; the proportion increased to 64% in 2008 and averaged 63% for 2008-2010. The proportion of institutionally funded clinical trials (derived from Indicator 2) for 2005-2007 was between 15% and 18%; in 2008, the proportion increased to 21% and averaged about 22% for 2008-2010.

The proportion of federally funded clinical trials (derived from Control 1) was between 24% and 29% from 2005 to 2007 (Figure 14). It decreased in 2008 to 15% and averaged about
15% in 2008-2010 (Figure 14). Therefore, the proportion of federally funded clinical trials relative to the total decreased because the share of industry-funded and institutionally funded clinical trials increased following Milestone 2 after the initial increase associated with Milestone 1.

Figure 15 plots the annual percent change relative to the previous year for the industry, federally and institutionally funded clinical trials of biologics for phase 2 and 3 combined. Federally funded clinical trials (Control 1) decreased in 2008 by 28%. In the following year of 2009, all three funding sources increased their number of clinical trials from the previous year; however, even though federally funded trials had the greatest annual increase of 23% in 2009, their relative proportion stayed largely unchanged at 17% (Figure 14).

Analysis of Figures 14 and 15 compares relative magnitudes of the response by the indicators to the 2007-2008 legislative negotiations over emerging biologics bill in the U.S. (Milestone 2). In response to the second milestone event, the magnitude of change for Indicators 1 and 2 in 2008 was notable (29% increase in Indicator 1 and 40% increase in Indicator 2), as measured by the annual increase in the number of clinical trials by Figure 15. While both Indicators 1 and 2 increased, Control 1 decreased in 2008 by 28%.

A possible reason why U.S. research institutions (Indicator 2) showed the greatest positive reaction to Milestone 2 (40% increase), while federally funded clinical trials decreased, may be that extramural NIH funds were shifted to biopharmaceutical research conducted by institutions. Consequently, federally funded research (Control 1) may have shifted from biopharmaceuticals to other research areas receiving less interest from industry (resulting in 28% decrease).
Milestone 2 – Indicator 3: FDA Approvals of BLAs

To determine if the U.S. biopharmaceutical industry responded to the 2007-2008 legislative negotiations over an emerging legislation for an abbreviated approval pathway for biologics in the U.S. (Milestone 2), the numbers of FDA approvals of biologics (Indicator 3) were measured and analyzed. Due to the 4.5-6.5 years lag between clinical trials and FDA approvals, the measurable response in Indicator 3 and Control 2 to this milestone event of 2007-2008 is expected to be delayed by about 6 years – around 2013-2014.

The average number of BLA approvals (Indicator 3) between 2009 and 2013 was about 6 per year (Figure 16). It increased to 11 in 2014, increasing further to 14 in 2015 (Figure 16). This increase occurred six years following Milestone 2 of 2007-2008 and corresponds with the expected 4.5-6.5 year time lag. From 2014 to 2016, the average number of BLA approvals was approximately 12 per year (Figure 16).

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Indicator 3 (Appendix 7) shows that FDA approvals of BLAs increased from an average of 6.8 to 9.7 per year. This increase is not statistically significant (P-Value = 0.295).

The number of new drug application (NDA) approvals (Control 2) ranged from 37 to 57 per year between 2009 and 2013 with an average of about 49 per year (Figure 17). In 2014, the number of NDA approvals increased to 71 and averaged approximately 69 per year for 2014-2016 (Figure 17). However, this new average of 69 was higher by 38%, compared to an increase by 100% for BLA approvals whereby the average number increased from 6 per year to 12 per year (Figure 16).
T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Control 2 (Appendix 7) shows that FDA approvals of NDAs increased from an average of 47.5 to 68.7 per year. This increase is not statistically significant (P-Value = 0.030).

Figure 18 plots the numbers of BLA approvals expressed as a percentage of the total number of all new drug approvals (BLA and NDA combined). The average proportion of BLA approvals from 2009 to 2013 was decreasing from a peak of 16% to a low 7%, averaging about 12% per year. In 2014, the percentage of annual BLA approvals doubled to 13% and continued to increase. For 2014-2016, the average proportion of BLAs was 15%. This increase, which began in 2014, occurred 6 years following Milestone 2 of 2007-2008 and corresponds with the expected time lag for FDA approvals.

The absolute increases in the raw number of BLA approvals (Indicator 3), as well as relative increases compared to NDA approvals (Control 2), occurred 6 years after 2007-2008 legislative negotiations for an abbreviated approval pathway for biosimilars in the U.S. (Milestone 2). This data supports Hypothesis 2, as measured by the change in the number of BLA approvals, that the U.S. biopharmaceutical industry responded favorably to the legislative negotiations regarding U.S. biologics approval pathway by increasing investment in research and development of biologics in anticipation of future legislation.

**Milestone 2 Conclusions**

Prior to 2010, there was no regulatory framework that would allow the FDA to approve biosimilar products. As Attorneys Ware and Littlefield of Foley Hoag, LLP wrote in 2008:
“Under current law, most biologics are licensed for marketing by the Food and Drug Administration under the Public Health Service Act. By contrast, small-molecule drugs are approved for marketing under the Federal Food and Cosmetic Act. The 1984 landmark Hatch-Waxman Act created an abbreviated pathway for approval, which allowed generic versions of brand drugs to be approved without clinical studies. … There is no such pathway available under the Public Health Service Act for biosimilar products, but several pending proposals in Congress would create such an abbreviated pathway for biosimilars, also known as Follow-on Biologics.”

Dalia Buffery, Senior Editorial Director of *American Health & Drug Benefits*, wrote: “We know that such a pathway is inevitable, and we know it is the way of the land to provide for competition and promote innovation. The bills for that new pathway have been circulating—with twists and turns—in Congress for some time now, but the legislation has been taking longer than the “normal route of innovation” dictates” (Buffery, 2010).

Some of the nation’s largest stakeholders joined to lobby Congress to pass legislation giving the FDA the needed framework for a biologics regulatory pathway, emphasizing that Europe provided such regulatory framework four years earlier. Among stakeholders were companies that provide health insurance to their employees. Annette Guarisco, Executive Director of Federal Affairs at General Motors stated: “We’re pleased that there's been a thoughtful debate in Congress on how to develop an FDA pathway for approving follow-on biologics. But at this point, we really need something that will affect the [spending] trend here. ... The generic market is already developing, but legislation could accelerate that” (Silverman, 2008).

One of the key negotiating points during the 2007-2008 discussions on Capitol Hill was the length of time for market exclusivity granted to innovator biotech companies for their
reference biologics to stimulate innovation in the field. As noted by Attorney Ude Lu, “the number of approved new drugs has decreased steadily in the past two decades. This steady decrease in innovation may justify twelve-year FDA exclusivity that provides a longer period of market monopoly and a higher profit margin for innovator drug companies” (Lu, 2014).

From the onset of the biosimilars talk in 2004, Biotech companies lobbied Congress for 12 to 14 years of exclusivity, though it was opposed by other stakeholders who were advocating for more accessibility (Silverman, 2008). Amgen’s Senior VP for Global Government Affairs David Beier was one of the earliest witnesses speaking on behalf of his company and trying to convince the Senate Committee on the Judiciary that protecting innovation, including data exclusivity, was key to spurring investment in breakthrough biologic medicines. He stressed the multibillion-dollar costs of pre-clinical and clinical trials and how the protection of this data is critical to biotech companies’ willingness to make the needed investment (Senate Hearing 108-635, 2004). As legislative negations over biologics and biosimilars were evolving, the necessity of exclusivity and the length of exclusivity period remained as one major sticking points where interests of multiple stakeholder groups had to be reconciled.

Representing the biotechnology industry at several Senate and House committee hearings was the Biotechnology Industry Organization (BIO) that offered arguments that exclusivity period of at least 12 years is necessary for the industry to commit to biologics innovation. In his written testimony, Attorney Jeffrey Kushan who acted as the spokesperson for BIO, emphasizing the need for stimulating and protecting biotechnology innovation through lengthy data exclusivity period. “BIO supports the creation of an abbreviated pathway for biosimilars to help increase competition among, and access to, the many breakthrough biomedical advancements that have been developed by the biotechnology industry over the past
25 years. In doing so, providing effective intellectual property protection for biological products must remain a central focus of Congressional efforts.” He went on to warn the lawmakers that the business environment in biotech industry will change once an abbreviated pathway for biosimilars products becomes available and that patent rights will not be sufficient to preserve the incentives for innovation” (House Hearing 111-73, 2009).

On the other side of the argument, there were many advocates of shorter exclusivity term and even no exclusivity at all. Those who took the anti-exclusivity position consisted of biogeneric manufacturers groups, consumer rights advocates and large employers and health insurers associations. While the main concern underlying their argument for less exclusivity was to allow more competition in the biologics marketplace to help contain costs of treatments, producers of follow-on biologics were making an argument that more competitive market would have positive effects on innovation in the industry. Senior VP and General Counsel for Momenta Pharmaceuticals Bruce Leicher said at the 2009 hearing of the House Subcommittee on Courts and Competition Policy that extensive exclusivity period would “promote low-risk, non-innovative development, and make biotech in the long run far less competitive.” He reasoned that to incentivize innovation data exclusivity should be limited because it would reward de-risking of product development portfolios of biotech companies since without the need to innovate they can get a product developed and, by virtue of getting the FDA approval, guarantee 12-14 years of exclusivity (House Hearing 111-73, 2009).

The data analyses for Milestone 2 indicates that indicators 1 and 2 (i.e., industry-funded clinical trials and institutionally funded clinical trials, respectively) responded favorably to the U.S. legislative negotiations by increasing the number of clinical trials of biologics in both absolute and relative terms. Indicator 3 (i.e., FDA approvals of Biologic License Applications) also increased
six years later. This data supports Hypothesis 2 that discussions by Congressional lawmakers and biotech stakeholders in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity by U.S. industry and research institutions in anticipation of an abbreviated pathway for biologics in the U.S.

From data analysis, the comparative magnitude of responses by indicators to Milestone 2 was greatest for institutionally funded clinical trials (Indicator 2). The fact that federally funded clinical trials (Control 1) decreased in response to the legislative negotiations of 2007-2008, suggests that extramural NIH funding shifted to the institutional biopharmaceutical research and federally funded research may have shifted from biologics to other fields where there was less interest by the industry. This observation also supports the causal linking between the Milestone 2 and R&D increase for industry and institutions (Indicators 1 and 2, respectively), since federally funded research activities do not rely on potential financial implications of the regulatory landscape.
Milestone 3:

The BPCIA is Enacted in March 2010

_Hypothesis 3_: the enactment of the BPCIA in 2010 resulted in increased biopharmaceutical research and development activity in the U.S. in response to the new regulatory pathway and the associated 12-year market exclusivity for biologics.

Data analyses

To determine if the U.S. biopharmaceutical industry responded to the enactment of the BPCIA (Milestone 3), the numbers of U.S. clinical trials for biologics (Indicators 1 and 2) were measured and analyzed.

_Milestone 3 – Indicator 1: Industry-Funded Clinical Trials of Biologics_

The combined number of phase 2 and 3 industry-funded clinical trials of biologics (Indicator 1) decreased in 2010 to 373 from its peak of 2009 and remained relatively flat, fluctuating between 357 and 426 until the end of the plotted period in 2016 (Figure 1). However, analyzing phases 2 and 3 separately, the data shows that phase 2 industry-funded clinical trials increased by 28% in 2011 from 205 to 263 (Figure 2). This increase was followed by two years of decline (217 in 2012 and 194 in 2013), though in 2014, the number increased again and averaged 259 per year in 2014-2016.
T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Indicator 1 (Appendix 4) shows that industry-sponsored clinical trials decreased from an average of 480 to 392 per year. This decrease is statistically significant (P-Value = 0.003).

Comparing the above data to federally funded clinical trials (Control 1), the combined number of phase 2 and 3 federally sponsored trials decreased in 2010 from 134 to 86 and continued to decrease in 2011 and 2012 (Figure 4). In 2013, the number of federally funded clinical trials increased to 90 and stayed relatively flat for the remaining period (till 2016), ranging from 82 to 104 (Figure 4). T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Control 1 (Appendix 5) shows that federally sponsored clinical trials decreased from an average of 122 to 84 per year. This decrease is statistically significant (P-Value = 0.019).

Analyzing phase 2 and phase 3 individually, the numbers of federally sponsored clinical trials in both phases followed the same pattern as the combined phase 2 and 3 number, decreasing for three years in a row from 2010 to 2012, then increasing in 2013 and remaining relatively flat (Figure 5).

The proportion of industry-funded clinical trials (Indicator 1), expressed as a percentage of federally funded trials (Control 1), increased in 2010 to from 363% to 434% and in 2011 it rose significantly to 595%, followed by another increase to 622% in 2012 (Figure 8). However, these years of increase of the relative proportion of the number of industry-funded clinical trials were followed by a decrease in the following years from 2013 to 2016, ranging between 396% and 490% (Figure 8).
Since the enactment of the BPCIA in 2010 (Milestone 3), the numbers of industry-funded clinical trials (Indicator 1) increased originally, supporting Hypothesis 3 and indicating a favorable response by U.S. biopharmaceutical companies to the new legislation. From 2013 however, the metrics for Indicator 1 returned to the levels before Milestone 3. A possible explanation to this is that lengthy and uncertain aspects of rulemaking by the FDA (which was slow to commence and is still ongoing, given the complex nature of the legislation and the intricacies of biologic products), resulted in a relative slowdown in biopharmaceutical research activities, specifically, phase 2 and 3 clinical trials. Future research needs to be done as BPCIA rules are promulgated and clarified by the FDA in the upcoming years.

Milestone 3 – Indicator 2: Institutionally Funded Clinical Trials of Biologics

While the combined number of phase 2 and phase 3 institutionally funded clinical trials (Indicator 3) increased slightly in 2011 from 141 to 148 (Figure 9), phase 3 trials increased by 80% from 25 to 45 trials (Figure 10). From 2013 to 2016, institutionally funded clinical trials experienced a sustained increase from 161 to 264 (Figure 9); this increase was due primarily to the 2013-2016 growth of phase 2 trials from 128 to 225 (Figure 10).

T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Indicator 2 (Appendix 6) shows that institutionally sponsored clinical trials increased from an average of 157 to 189 per year. This increase is not statistically significant (P-Value = 0.390).

By comparison, the combined number of phase 2 and 3 federally funded clinical trials (Control 1) decreased in 2010 by 36% from 134 to 86 and continued to decrease in 2011 and
2012 (Figure 4). In 2013, the number of federally funded clinical trials increased by 50% to 90 trials and stayed in a relatively flat range till 2016, fluctuating between 90 and 104. The numbers of trials in both phases 2 and 3 followed a similar pattern, decreasing for three years from 2010 to 2012 before increasing in 2013 and staying in a flat range (Figure 5).

To compare the indicator and the control, Figure 12 plots institutionally funded (Indicator 2) and federally funded (Control 1) phase 2 and 3 clinical trials side-by-side, while Figure 13 plots the same values expressed as a percentage. Before the BPCIA enactment in 2010 (Milestone 3), institutionally funded clinical trials outpaced federally funded trials at 142% in 2008 and 119% in 2009. In 2010, this percentage proportion increased to 164% and continued to grow for two years peaking at 280% in 2012. This was followed by a moderate decrease and fluctuating between 179% and 275% from 2013 to 2016.

Since the enactment of the BPCIA in 2010 (Milestone 3), the number of institutionally funded clinical trials (Indicator 2) originally increased very moderately and slowly; however, from 2014, this increase accelerated as the number climbed steadily for the last three observed years. This data supports Hypothesis 3 by showing a favorable response by U.S. research institutions to the new legislation. The fact that this favorable response was not as strong in the first three years after the milestone event may be attributed to the uncertain and lengthy rulemaking by the FDA.
Milestone 3 – Indicators 1 vs. 2 vs. Control

To compare relative magnitudes of the response of the indicators to the enactment of the BPCIA in 2010 (Milestone 3), Figure 14 plots the relative proportions of phase 2 and 3 clinical trials funded by industry, research institutions and federal government (Table 3, Table 4 and Table 5).

In 2009 and 2010, the proportion of industry-funded clinical trials (derived from Indicator 1) was approximately 62%. In 2011, it increased to 69%, before gradually decreasing each year, finishing at 52% in 2016 (Figure 14).

The proportion of institutionally funded clinical trials (derived from Indicator 2) increased in 2010 to 24% (from 20% in 2009) and then increased again to 28% in 2012. It continued to increase each year and by 2016 institutionally funded phase 2 and 3 clinical trials comprised 35% of all stage 2 and 3 clinical trials (Figure 14).

Comparing the proportion of federally funded trials (derived from Control 1) to those of Indicators 1 and 2, their proportion decreased in 2010 to 14% (from 17% in 2009) and stayed in a range of 10-13% for the remaining years (Figure 14).

In summary, in response to Milestone 3, the proportion of industry-funded phase 2 and 3 clinical trials (Indicator 1) increased originally in 2011 before decreasing each subsequent year, the proportion of institutionally funded trials (Indicator 2) steadily increased year after year, while the proportion of federally funded clinical trials (Control 1) decreased over three years and then fluctuated in a relatively flat range.
Figure 15 plots the annual percent change relative to the previous year for the industry, federally and institutionally funded clinical trials of biologics for phase 2 and 3 combined. In 2010, all three funding groups decreased their clinical trials with federally funded trials (Control 1) decreasing the most (by 35%) and institutionally funded trials (Indicator 2) decreasing the least (by 11%). However, in 2011, industry-funded and institutionally funded trials increased (by 13% and 5%, respectively), while federally funded trials decreased further by 17% and again in 2012 by about 16% (Figure 15).

Comparing the relative magnitudes of the response of the indicators to the enactment of the BPCIA in 2010 (Milestone 3), federally funded clinical trials (Control 1), after 3 years of decreases (2010-2012), fluctuated with the absolute number staying in a flat range (Figure 4), while industry-funded trials originally responded by increased clinical trials in 2011 and then slowed and fluctuated in a relatively flat range. Institutionally funded clinical trials exhibited the strongest favorable response to Milestone 3 with an overall increase of 87% from 141 trials in 2010 to 264 trials in 2016.

A possible reason why U.S. research institutions (Indicator 2) showed the greatest reaction to Milestone 3, may be that biopharmaceutical companies being active in both innovative reference biologics and biosimilars were faced with an obstacle to their biosimilar products due to high regulatory burdens and similarity requirements by the FDA. Research institutions, being active primarily in the field of novel products, increased their R&D activity (as measured by the number of phase 2 and 3 clinical trials). Nevertheless, biopharmaceutical companies were still a leader in the absolute number of clinical trials of biologics since 2005 till 2016, comprising between 52% and 66% of all phase 2 and phase 3 trials of biologic products (Figure 14).
Milestone 3 – Indicator 3: FDA Approvals of BLAs

Since FDA approvals lag the commencement of clinical trials by an average of 4.5-6.5 years, at the time of data collection and conducting of this study, there was not enough data to analyze a measurable response in Indicator 3 and Control 2 to Milestone 3 and draw conclusions whether the U.S. biopharmaceutical industry responded to the enactment of the BPCIA.

As of the time of this study, FDA approvals of BLAs for 2016 equaled 12, which is 2 fewer than the peak of 14 in 2015 attributed to the response to Milestone 2 (Figure 16). The proportion of BLA approvals as a percentage of all BLA and NDA approvals continued to increase in 2016 to 17% (Figure 18), which may or may not be attributed to Milestone 3.

The number of BLA applications submitted to the FDA for review and approval would be helpful for extrapolated analysis, but FDA does not make this data available. However, at the 2009 appropriations hearing in front of the Senate Subcommittee on Agriculture, Rural Development, FDA, and Related Agencies, Acting FDA Commissioner Dr. Joshua Sharfstein predicted: “We also anticipate receiving some applications for review shortly after enactment of [biosimilars] legislation, with an increasing number of applications for review in subsequent years” (Senate Hearing 111-252, 2009). As of 2008, there was a rich pipeline of biologic product candidates in discovery and development from a spectrum of small start-up firms to larger established companies. But most of this pipeline emanated from firms without marketed products whose investors are very sensitive to expected future returns and risks (Grabowski, Long & Mortimer, 2008).
In summary, more data for FDA approvals from the upcoming years is needed for future research to support or refute Hypothesis 3 as measured by the number of FDA approvals of biologics.

**Milestone 3 Conclusions**

The BPCIA was enacted to provide biologics and biosimilars with the regulatory pathway for FDA approval. It was aimed at achieving two public policy objectives. Attorney Ude Lu writes: “The central mission of the BPCIA is two-fold: (1) providing sufficient incentives for continuous innovations in biologic therapies (i.e., promoting innovation); and (2) lowering the price of biologic therapies (i.e., promoting accessibility)” (Lu, 2014).

The main incentive for innovation was created through 12-year exclusivity period granted to innovator companies for novel biologic drugs. This widely accepted notion was expressed by many authors, including patent attorney Katherine Addison who writes: “Longer FDA exclusivity times, including the twelve-year period for biologics specified in the recently passed BPCIA, should help to encourage investment in biologics. The FDA exclusivity period alone will not be long enough to recoup all of the investment required to develop and obtain approval for many biologics and other inventions, however, it does provide some level of guaranteed exclusivity while awaiting a response from the PTO regarding patentability. This independent exclusivity should encourage companies to get their FDA applications moving forward earlier and for products that are approved it will reduce potential economic loss thereby supporting investment” (Addison, 2011).
In addition to exclusivity period, the competition structure between innovator companies and follow-on biologic manufacturers was also set up with the underlying objective of stimulating innovation while increasing access to biologic products. Senior Editorial Director of *American Health & Drug Benefits*, Dalia Buffery summarized this competition scheme by writing “the FTC concludes that the introduction of biosimilars will emulate brand–brand drug competition rather than brand–generic drug competition, and that patent protection and market-based pricing will promote competition by FOBs, as well as spur biologic innovation” (Buffery, 2010).

The data analyses for Milestone 3 demonstrates that Indicators 1 and 2 responded differently to the enactment of the BPCIA, while Indicator 3, due to its time lag, could not be reliably analyzed at the time of this study.

Since the enactment of the BPCIA in 2010, industry-funded clinical trials (Indicator 1) increased originally. However, from 2012 the numbers dropped back, possibly because of the uncertainty and delays in the FDA rulemaking, as well as regulatory burdens placed by the Act on manufacturers of biologics intended to be follow-on versions of reference products. Industry news reported that some companies halted their biosimilars development in response to the BPCIA enactment. As Ganesh Kaundinya, Chief Scientific Officer and co-founder at biologics and biosimilars developer Momenta Pharmaceuticals said: “This is not for the faint of heart. This is for somebody who is really committed to going into it with deep pockets and wants to stay in it for several years before they can know the answer to it” (Palmer, 2013).

Research institutions responded with an increase in the number of clinical trials (Indicator 2), though this increase started off relatively slow and accelerated by 2014, exhibiting the greatest comparative magnitude of responses to Milestone 3. A possible reason for this may be that many
biotech companies active in both innovative reference biologics and biosimilars were now faced with an obstacle to their biosimilar products due to high regulatory burdens and similarity requirements by the FDA. Research institutions, however, increased their R&D activity because they are active primarily in the development of novel products (reference biologics).

Therefore, responses by Indicator 1 and Indicator 2 to Milestone 3 support the Hypothesis 3, though only as it pertains to innovative biologic drugs. Enactment of the BPCIA in 2010 was followed by an increase in biopharmaceutical research and development activity in the U.S. While the causality cannot be established with absolute certainty, it is likely that this reaction was produced in response to the market exclusivity given to innovator companies, fulfilling the BPCIA’s policy objective of stimulating innovation.

However, developers of follow-on biologic drugs (i.e., biosimilars) appear to be faced with very high regulatory burdens for the approval of their products. This leaves the other objective of the BPCIA – reduction of treatment costs – to be fulfilled. Additional research needs to be conducted in the future, as BPCIA rules are issued and clarified by the FDA, as well as more historical data becomes available for study, to better understand the scope and magnitude of impact by the BPCIA on U.S. biopharmaceutical companies.
Conclusions of the Study

In the new age of biotechnology and biologic medicines, the Biologics Price Competition and Innovation Act of 2009 is a landmark policy that regulates this large sector of the U.S. economy and the leading treatment modality for patients suffering from debilitating conditions. The BPCIA did not happen suddenly; two other leading events preceded it, which created the anticipation and triggered events that ultimately lead to the enactment of the new U.S. biologics law in 2010.

While the European Union adopted a pathway for biosimilars in 2004, the U.S. did not have such a pathway, despite being a world leader in biotechnology research. Congress and policy analysts have recognized the lack of a similar abbreviated approval process for biologic products as an impediment to innovation and introduction of less expensive therapies. A new regulatory approval pathway for biosimilars was needed because biologics are not regulated under the Hatch-Waxman Act, therefore they are not subject to the Act’s accelerated FDA approval. Neither were biosimilars covered by the state laws that allow automatic substitution at a pharmacy.

In this research, I examined how the three sequential phases (i.e., milestones) of the emergence and implementation of BPCIA affected biopharmaceutical research in the United States. Specifically, how these milestone events affected biopharmaceutical innovation as measured by 1) the number of clinical trials and 2) the number of FDA approvals of new biologic license applications (BLAs).

In this study, I compiled and analyzed data that intersects these three milestones (i.e., independent variables) with three indicators (i.e., dependent variables), where Indicator 1 is the
number of industry-funded clinical trials, Indicator 2 is the number of institutionally funded clinical trials and Indicator 3 is the number of FDA approvals of BLAs. Measurable responses by these three indicators in response to each milestone demonstrate how the expectation and realization of the BPCIA impacted the biopharmaceutical industry in the United States and the data is used to support the three hypotheses of the study.

This study is the first attempt to bring empirical evidence to study the topic of the effects of BPCIA exclusivity provisions on biopharmaceutical innovation. While the conclusions of this research may not be taken as exhaustive, they provide a valuable platform for further investigation. And while observed correlations do not necessarily establish causation, this research analyzes the response of biopharmaceutical R&D via data closely associated with innovation. As biopharmaceutical industry expands and more data becomes available, further analysis is needed to quantify the impact of the BPCIA on biopharmaceutical innovation.

Milestone 1 was when the European Union enacted a new legislation to create a statutory pathway for approval of biosimilars in 2004. European biologics pathway was developed between 2003 and 2004 and went into effect in 2005. In 2006 Europe had its first biologic drug approved under the new regulations. The U.S. biotech industry looked to Congress to get a corresponding legislation in the U.S. and at one of the earliest biologics hearings, Senator Schumer said: “Surely, if the science is adequate to produce these products elsewhere, especially in Europe where the system of regulation, as I mentioned, is similar to ours, we can do it here. So we have got to get the process rolling” (Senate Hearing 108-635, 2004).

In 2006, the Consumers Union urged the Senate Committee on Health, Education, Labor, and Pensions to follow the EU’s lead because there was no law providing for the approval
of follow-on versions of biologic medicines. The union’s CEO and President Jim Guest expressed the anticipation for an opportunity to provide cost savings and safe treatments patients in need if the U.S. emulates the European law (Senate Hearing 109-850, 2006).

The data analyses for Milestone 1 demonstrated that the three indicators of innovation – industry-funded clinical trials (Indicator 1), institutionally funded clinical trials (Indicator 2) and FDA approvals of Biologic License Applications (Indicator 3) – responded favorably to the milestone, supporting my first hypothesis that development and enactment of the biosimilars legislation in Europe in 2004 triggered an increase in biologics R&D investment by the U.S. biopharmaceutical industry in anticipation of similar legislation developing in the U.S. The number of industry-funded and institutionally funded clinical trials (Indicators 1 and 2) increased in the absolute and relative terms. The number of FDA approvals of biologic license applications (Indicator 3) also increased measurably five years later, which is the expected time frame for this lagging indicator.

Industry-funded clinical trials (Indicator 1) showed the greatest magnitude of positive response among all three indicators, which is due to the fact that biopharmaceutical companies likely had the greatest interest in the prospect of new biologics legislation for the U.S. and the commercial potential that it would bring to manufacturers of biologic medicines.

Following the EU biologics law enactment, negotiations between members of Congress and the stakeholders ensued in 2007-2008 (Milestone 2). Using the European law as an example, interest groups (including biotech companies, ensures and pharmacies) were pushing for crafting and enactment of a separate pathway of regulatory FDA approval of biologics. Congress listened to these requests and invited Dr. Nicolas Rossignol, a Senior Administrator of
the European Commission Pharmaceuticals Unit, to one of the hearings. Dr. Rossignol, among other things, spoke about the importance of involving the industry, as well as other interested parties (e.g., patients associations, healthcare professionals), into the process of crafting the legislation. He said that this approach allowed European policymakers at the EMEA/European Commission to use the expertise in the field and to compare their vision with the practical experience of manufacturers and healthcare providers. Moreover, involving both sides of the industry enabled them to have a “constructive exchange of contradictory views and facilitated the development of a balanced, unbiased regulatory framework.” Dr. Rossignol added: “Transparent involvement of both the generics/biosimilar and the innovative industry, together with strong assurance of the independency of the scientific experts involved in the establishment and implementation of the regulatory framework, are in my opinion key factors to ensure that legitimate scientific issues are considered but dilatory tactics do not derail the process” (Senate Hearing 110-375, 2007).

For this Milestone 2, my data analyses also showed a favorable response by all three indicators, supporting my second hypothesis that discussions by U.S. lawmakers in 2007-2008 pertaining to the separate approval pathway for biologics resulted in increased biopharmaceutical research and development activity in the U.S. in anticipation of an abbreviated pathway for biologics in the U.S. The number of industry-funded and institutionally funded clinical trials (Indicators 1 and 2) increased in absolute and relative terms in response to Milestone 2. FDA approvals of BLAs (Indicator 3), being the lagging indicator of innovation, also registered an increase that was delayed by six years.

Institutionally funded clinical trials (Indicator 2) exhibited the greatest magnitude of positive response to Milestone 2. Combined with the decrease in federally funded clinical trials
(Control 1), it is likely that a larger portion of NIH’s funding grants shifted to biopharmaceutical research projects conducted by institutions while federally funded research focused more on other research areas where there was less activity from industry despite the existence of a public need.

After Congress passed the bill in late December 2009, the BPCIA was signed into law by President Obama in March 2010 (Milestone 3). The enactment alone did not immediately shape the new regulatory landscape for biologics. Given their complex nature and many scientific, manufacturing and legal intricacies, the FDA took time to issue rules and guidances to create a clear framework for the stakeholders to work within. Feedback from industry’s players was sought and incorporated into FDA’s rulemaking. This delay created many questions and uncertainties within the industry for the first few years following the law’s enactment.

After the BPCIA was enacted in 2010, there was much debate and speculation within the biopharmaceutical industry about what was coming and what new challenges the Act could face as rules and comments were slowly rolling out by the FDA over the period of the first five years. In 2012, Dr. Bao-Lu, Director of Manufacturing and Process Development at Sangamo BioSciences, wrote: “We anticipate the package for a biosimilars approval in the US will be similar to that in the EU and contain a full quality dossier with a comparability program including detailed product characterization comparison and reduced preclinical and clinical requirements” (Bao-Lu, 2012).

In August of 2014, Attorneys Janet McNicholas and Tamera Weisser wrote: “Although the BPCIA was enacted into law more than four years ago, it should not be surprising in view of these uncertainties surrounding regulatory approvals that only two applications for biosimilars
have been recently submitted, both for products that have already been approved and marketed as biosimilars in many other countries. On July 24 [2014], Sandoz Inc., a unit of Novartis AG, announced that the FDA had accepted its application for a biosimilar for Amgen’s Neupogen... The FDA acceptance was a U.S. landmark in that it is widely believed to be the first of any biosimilar application. More than 40 countries have already approved the biosimilar, which is marketed by Sandoz as Zarxio. On August 11 [2014], South Korea-based biosimilar manufacturer Celltrion Inc. announced that the company is seeking FDA regulatory approval of Remsima as a biosimilar for Johnson & Johnson affiliate Jenssen Pharmaceutical’s Remicade… More than 50 countries already issued regulatory approval for Remsima… Having proven “biosimilarity” under the EMA biosimilars pathway, both the Sandoz and Celltrion biosimilar products are believed to have the higher chance than most for success under the new U.S. licensure pathway” (McNicholas & Weisser, 2014).

Following the enactment of the BPCIA in 2010 (Milestone 3), industry-funded clinical trials (Indicator 1) increased originally before retracing in 2012. It is very likely that the uncertainty and delays in the FDA rulemaking contributed to this lack of momentum within biotech companies.

However, institutionally-funded clinical trials (Indicator 2) increased in response to the enactment of the BPCIA. While the increase was originally tepid, it accelerated in 2014, demonstrating the greatest favorable response to Milestone 3. This difference in reactions between biotech companies and research institutions can be understood when analyzing the specifics of operations within these two categories. Biopharmaceutical companies interested in both novel reference biologics and follow-on biosimilars were now sorting through regulatory burdens placed on the approval of biosimilar products.
Research institutions, however, are active in the space of development of reference biologics and therefore their innovation levels, as measured by the number of clinical trials, increased. This supports my Hypothesis 3 that enactment of the BPCIA in 2010 resulted in increased biopharmaceutical research and development activity in response to the new regulatory pathway and the associated 12-year market exclusivity for biologics. However, it is important to note that this increased R&D activity pertains to new biopharmaceutical discoveries, thereby achieving one of the primary public policy objectives of BPCIA – stimulating innovation.

The second major objective of BPCIA was to lower healthcare costs by making biologics more affordable though providing a separate approval pathway for biosimilars. This goal is not achieved at this time because developers of biosimilars must be able to overcome several major hurdles to be able to go through the approval process under the new rules. One of these hurdles is qualifying the drug as a biosimilar. The BPCIA and the FDA rules set a very strict set of standards of biosimilarity and even stricter standards for interchangeability.

As part of the process, biosimilars’ developers must undertake extensive clinical trials to prove similarity – something that small-molecule generic manufacturers don’t have to do. This adds more development costs to an already expensive and complicated process of biologic manufacturing. According to IMS Health, development of generic small-molecule drug costs from $1 million to $4 million, while the cost of developing a biosimilar ranges from $100 million to $250 million (Gray, 2015).

Nevertheless, certain clarifications contained within the FDA guidance may allow manufacturers of biosimilars to be able to reduce their costs and streamline the approval process. FDA Practice Group Leader, Co-Chair of Life Sciences Industry and former FDA
staff member David Rosen states: “The new Guidances provide developers of biosimilar products with a framework that provides an organized, systemic approach for the development of these types of products. By providing the Guidances, the Companies can gain a better understanding of FDA’s expectations which can lead to more efficient and lower development costs” (Gray, 2015).

In its guidance for biosimilar producers issued in April 2015, the FDA states that biosimilars may be formulated differently than the reference biologic; however, to apply for FDA approval, sponsors must provide data showing that these formulation differences did not result in “meaningful differences” in safety, purity and potency (Gray, 2015). Kate Keeping, senior director of biosimilars research at Decision Resources Group, said: “One way to reduce costs is by doing as few trials as possible. One possibility would be to design a three-arm trial, comparing the biosimilar in development with a U.S. reference product, and an E.U. reference product” (Gray, 2015).

Despite more regulatory guidance now available from the FDA, not all details of the new regulatory pathway are yet flushed out by the regulators. Chip Davis, President and CEO of Generic Pharmaceutical Association (GPhA), in his statement on February 4, 2016 issued in response to the first Congressional oversight hearing since the enactment of the BPCIA held by the House Energy and Commerce Committee proclaimed: “Additional clarity from currently outstanding FDA guidances on interchangeability, extrapolation and labeling are each critical to the timely availability of biosimilars in the United States. The [Biosimilars] Council urges the agency to issue these guidances promptly” (Davis, 2016).
At a time of legislative negotiations, there was a hot debate regarding the 12-year market exclusivity for reference biologic drugs. Various industry interest groups advocated for a shorter period of exclusivity citing the need for lower healthcare costs as a concern. Representative Henry Waxman who opposed 12-year exclusivity before and after the enactment of BPCIA as part of the Affordable Care Act, when speaking at a generics industry conference, stated: “I believe the biosimilar provisions of the Affordable Care Act unfortunately fell far short of assuring that innovation will be balanced with competition. As a result, the generic medicines market will, I fear, not expand in the area of biologics in as robust a manner as should be possible, no matter how well the FDA implements its biosimilars program” (Foxhall, 2012).

Ultimately, biopharmaceutical companies won the argument of longer exclusivity periods for the sake of stimulating innovation. President and CEO of the Biotechnology Industry Organization (BIO) Jim Greenwood, in his press release issued in response to data exclusivity period negotiations over the Trans-Pacific Partnership Agreement, wrote: “The current 12-year period of exclusivity in the United States was carefully crafted by a bi-partisan majority of the Congress after a thorough and thoughtful debate and deliberation. The Congress set 12 years as the appropriate period to both foster innovation and provide access to biosimilars in a reasonable timeframe” (Greenwood, 2015).

Other points of contention between brand-name biologic and biosimilar manufacturers include interchangeability, pharmacy substitution and notification requirements. While biosimilars naming will eventually be settled by the FDA, the agency left substitution and notification requirements up to the states to regulate. Biosimilars’ developers are concerned that state laws that would mandate pharmacist notification or limit interchangeability aiming to protect patient safety could diminish cost savings to individuals, employers and insurers (Barlas, 2014).
Limitations of the Research

Establishing and proving causality in the field of social sciences is always difficult for researchers because it is often impossible to isolate and neutralize confounding variables. This makes it troublesome to state that a certain event is the sole cause of the outcome. In this research, I attempt to identify the response of a whole industry to a series of policy events via measuring three indicators closely tied to innovation in the industry. Establishing causation based on identified correlation proves to be challenging since innovation in biopharmaceuticals is affected by many factors, including, but not limited to, new discoveries in scientific knowledge, availability of novel technologies, access to private capital and public funding and the general state of the economy.

Despite these challenges and considerations, and acknowledging the aforementioned factors, this research offers a perspective on the sensitivity of selected metrics of biopharmaceutical innovation to events associated with the new regulatory landscape. As emphasized throughout this paper, the BPCIA was implemented with the dual goal of stimulating innovation and improving access to biologic medicines. This dual mission is incorporated in the title of the Act by the words “Price Competition and Innovation.”

The U.S. law was preceded by a prototype regulation enacted in Europe five years earlier with the same dual legislative agenda. For stimulating innovation European regulators provided 10-year exclusivity period (with additional one year for certain cases). As European biologics law has been in place longer than BPCIA, commentators are attempting to assess its success in encouraging biopharmaceutical innovation in Europe whereby the general agreement is linking the legislation to increased innovation. Researchers Jacques Pelkmans and Andrea Renda
acknowledge that “the interaction between regulation and innovation is complex, multifaceted, and often ambiguous, such that assessing the impact of a given piece of regulation on innovation is often an empirical, case-by-case exercise.” Nevertheless, they conclude, among other things, that “EU regulation matters at all stages of the innovation process, from R&D to commercialization” (Pelkmans & Renda, 2014).

Currently, the European Union is considered to be the world leader in biosimilar progress where the majority of R&D, clinical trials, applications, approvals, manufacturing and product revenue related to biosimilars is taking place (Rader, 2017). The European Medicine Agency (EMA) declared its objectives to be active in ensuring that it embraces scientific advances in an effort to stimulate rather than hold back innovation. With biosimilars, Europe is now a global leader to a large extent due to the availability of a regulatory framework, which first started to be put in place more than 10 years ago (Milmo, 2014).

The United States went even further than its European counterparts in encouraging innovation by providing a 12-year exclusivity period for innovator biologics. Attorney Ude Lu expressed the general agreement on the connection between exclusivity and innovation when he wrote: “The general public benefits from the innovation of new biologics because they provide life-quality improving treatments that did not exist before. It is important for the government to offer proper incentives to ensure innovator drug companies in recouping the heavy investments and ensure their ability to fund new research to continue innovation. Commentators view the twelve-year FDA exclusivity provided in 42 U.S.C. § 262(k)(7)(A) to be the most important and effective measure in the BPCIA to promote innovation” (Lu, 2014).
In addition to this step, FTC also predicted in its 2009 report that introduction of biosimilars will “promote competition by FOBs, as well as spur biologic innovation” by creating a framework for the brand–brand drug competition rather than for brand–generic drug competition (FTC, 2009). This prediction is rooted in the foundational free-market principle that “more is better” and competition introduced by biosimilar drugs will encourage rather than deter innovation. If the FTC is correct that competition stimulates innovation, in this case, everyone is poised to win: patients, payers and drug manufacturers (Buffy, 2010).

As this research is subject to an inherent challenge of proving causality, in my attempt to evaluate whether the new biologics approval pathway law achieved its goal of stimulating innovation, I used a multi-faceted approach. Rather than simply measuring indicator response to a single milestone event of BPCIA enactment in 2010, I measured responses to two other preceding milestones: enactment of European regulation and congressional negations in the U.S. This approach allowed me to observe certain consistency in indicators’ reactions suggesting that these reactions were likely caused by the milestones. Furthermore, I was able to designate three separate, but interrelated, indicators of biopharmaceutical innovation which exhibited parallels and differences in reacting to milestones events that are reasonably explained by the specific impact of each milestone rather than random variance. Using T-tests, I determined statistical significance, or lack thereof, in the reactions of each indicator and control. Lastly, the controls (federally funded clinical trials and FDA approvals of NDAs) used for normalizing the data to quantify measured responses by indicators further strengthened the cause-effect linking within the conclusions of my research.
Future Challenges for Biosimilar Litigation

Since the enactment of the Hatch-Waxman Act in 1984 and until recently, there has not been as much concern or speculation on the legal and economic impact on branded drugs and manufacturers. Competition among pharmaceutical companies has increased considerably since the passage of the Hatch-Waxman Act in 1984. The amendment to the Food Drug, and Cosmetic Act has given rise to an increase in both the rates of generics and patent litigation (Grabowski, Long & Mortimer, 2014). The Hatch-Waxman Act created incentives for generic manufacturers to challenge brand-name patents before they expired by use of a Paragraph IV ANDA (Abbreviated New Drug Application) where the generic drug manufacturer notifies the FDA that either its generic product does not infringe on the listed patents or that the patent held on the brand-name product is invalid (Grabowski et al., 2014). The first generic to file a Paragraph IV challenge and to receive FDA final approval is granted a 180-day period of exclusivity. This period is generally very profitable to a generic manufacturer because the generic drug manufacturer tends to drop price only modestly below the brand-name drug and often the generic-brand market share increases rapidly (Grabowski et al., 2014). The Congressional Budget Office (CBO), in 1998, reported that generic-drug competition reduces the net present value of the total stream of future profits to brand-name manufacturers by an estimated 12%. The report concludes that the negative effects on profits by generics competition outweigh the positive effects of patent term restoration permitted under the Hatch-Waxman Act (Grabowski, et al., 2014).

Because of the key differences between follow-on biologics and generic drugs, it is unclear what the litigation landscape will look like. Due to the number of associated patents used in the manufacturing process, it is likely that the potential for lawsuits is great (Frois, et al.,
2016). Even with a low number of biosimilar applications (i.e., 57 as of September 2016), there have already been filed several patent infringement lawsuits. These lawsuits have sparked a debate on the validity of the associated patents and the process for patent litigation under the BPCIA (Frois, et al., 2016).

Although early in the licensing cycle, biosimilar applications with the FDA have already raised questions about the specifics of the Act (e.g., data exclusivity, clinical trials and naming), allegations of patent infringement and antitrust violations have resulted in several lawsuits (Frois, et al., 2016).

In recent years, the entry of generic drugs has spawned increased litigation of intellectual property disputes and alleged antitrust violations. Between 2011 and 2014, more than 90 percent of initial generic drug entries into the marketplace had one or more patent challenges associated with their application as a generic (Grabowski et al., 2016). The litigation stemming from generics often involves economic questions such as class certification, market definition and damages. As biosimilars enter the market, the question is whether similar litigation awaits manufacturers of biosimilars. The answer is more complex because of both the economics of biosimilars (e.g., market penetration and price discounts) and some important regulatory differences between small-molecule (chemical) drugs and large-molecule (biologic) drugs (Frois, et al., 2016).
Ongoing Political Debate

Since the enactment of BPCIA in 2010, there were (and still are) continued political and legislative efforts to repeal the 12-year exclusivity provision. Since 2010, President Obama tried to reduce the period of data exclusivity through budget proposals from 12 to 7 years. These efforts have also been a part of the struggle to pass the global Trans-Pacific Partnership (TPP) trade agreement which called for a 5-to-8-year exclusivity period for the U.S. law to be more in line with other countries (Mukherjee, 2016).

President Obama’s 2015 budget proposal, which again included the reduction of exclusivity to 7 years, cited estimated savings of 700 million dollars in healthcare spending as the major reason for the modification. This action was supported by the Generic Pharmaceutical Association (GPhA) and its CEO Ralph Neas claimed that potential savings could be even higher “with some groups predicting more than $250 billion in savings over 10 years” (Stanton, 2014).

Industry’s BIO responded with a statement which highlighted the potential threat of discouraging innovation: “The 12-year term of data protection for biologics included in the Affordable Care Act received widespread bipartisan support in the Congress during the consideration of the biosimilar pathway and is now settled US law. A reduction in this period will jeopardize the careful balance established in the law to reduce costs, expand access, and encourage continued innovation that will create good, high-paying biotech jobs and lead to breakthrough therapies and cures for deadly diseases” (Stanton, 2014).

The Pharmaceutical Research and Manufacturers of America (PhRMA) joined the opposition to the proposed measure of reducing exclusivity by asserting that the President’s
Budget “unproductively pushes, yet again, previously rejected proposals that would hurt, not bolster, the program” (Stanton, 2014).

In June of 2016, a bi-partisan group of Senators and House Representatives introduced the Price Relief, Innovation, and Competition for Essential Drugs Act, again attempting to decrease the exclusivity term to 7 years (Brennan, 2016). This effort was intensely opposed by major trade groups like the BIO, which argued that anything less than 12 years of exclusivity would stifle innovation, reduce drug access and ultimately increase prices in the long term. The BIO’s Vice President for Federal Government Relations, Jeanne Haggerty, wrote in a statement: “This legislation would disrupt the careful balance, created by Congress with broad, bipartisan support in the Biologics Price Competition and Innovation Act (BPCIA), between the need to encourage investment in innovative, groundbreaking biological therapies and the desire to ensure that patients have increased choices offered by biosimilar products after a reasonable period of exclusivity for the innovator product. The majority of biotechnology companies are small, private start-ups, heavily reliant on venture capital investment. And these companies hold two-thirds of the industry’s innovative clinical pipeline. Undermining investment in these companies means undermining investment in the next biomedical breakthroughs for patients. The legislative process that produced the current U.S. system was deliberate, thoughtful, and driven by rigorous analysis. The BPCIA received overwhelming support in Congress at the committee level and in both the full House and Senate. This legislation is a short-sighted attempt to undercut the critical work that innovator companies are doing and would, if enacted, deprive patients of many new treatments and cures in the future” (BIO, 2016).
Naturally, the GPhA expressed a diametrically opposing view claiming that the legislation would “speed patient access to more affordable versions of some of the most expensive medicines. As brand and specialty drug costs rise at a concerning rate, the association looks forward to working with Congress and others to ensure timely access to biosimilar medicines” (Mukherjee, 2016).

It is worth mentioning that the biologics industry has also tried to push for more than 12 years of exclusivity since the BPCIA’s enactment. In 2014, US senators Orrin Hatch and Michael Bennet have proposed the bill known as the Dormant Therapies Act of 2014 that would grant an unprecedented 15 years of marketing exclusivity to certain types of pharmaceutical and biopharmaceutical products. The act (advocated for by the pharmaceutical manufacturer Eli Lilly) would create a new Dormant Therapy designation modeled after FDA’s other existing designation programs intended to offer designees special incentives, such as added periods of marketing exclusivity and additional support (i.e., fast-track) during the FDA review process (RAPS, 2014).

The bill ultimately did not pass and was met with heavy criticism by some witnesses at the June 2014 hearing of the House Subcommittee on Health of the Committee on Energy and Commerce. Dr. Steven Miller, Senior Vice President and Chief Medical Officer for Express Scripts Holding Company, expressed a concern that the burden of increased costs created by a wide range of products qualifying for long-term exclusivity would fall on employers and health plans. He claimed that that statutory exclusivity would create perverted incentives for the commercial market and actually hinder innovation by artificially limiting competition (House Hearing 113-151, 2014).
Professor of Law at the Columbia University Law School, C. Scott Hemphill, in his testimony, spoke about the breadth of the statutory inclusion criteria for a Dormant Therapy designation and argued that under FDA’s definition of an “unmet medical need,” too many products that would otherwise have sufficient market forces would prevent generic competition (House Hearing 113-151, 2014).

**The Potential for Future Research**

For this study, I focused on clinical trials and FDA approvals as metrics of innovation in biopharmaceuticals. As this economic sector grows further and the outcomes of the BPCIA become clearer, more research is needed to answer definitively whether the new law is successful in achieving the goal of stimulating innovation. Future researchers may add other metrics of innovation.

One such metric of innovation can be R&D spending. Although public funds are awarded for basic research, the discovery and development of new biopharmaceuticals require large privately-financed expenditures. The research and development expenditures – of individual companies and as an industry aggregate – may be used by researchers as a measure of the confidence that biopharmaceutical firms have in innovation to develop new profitable products (Scherer, 2007). Stronger market exclusivity protections increase the profits available to the manufacturer for more R&D spending on new products.

Biopharmaceutical R&D has two distinct phases: pre-clinical and clinical. Pre-clinical R&D involves expenditures on laboratory development of pharmaceutical molecules and the
initial testing on animals. Clinical R&D includes the investment needed for testing the newly
developed therapeutic on human subjects to establish safety and efficacy as required for FDA
approval (DiMasi, Hansen, & Grabowski, 2003).

Future research may use pre-clinical R&D as a metric of innovation activities by
biopharmaceutical companies. Pre-clinical research expenditures may be a strong indicator of
innovative activities within the biopharmaceutical industry because it is in pre-clinical phase
when novel molecules are discovered.

Clinical R&D may also be used as an individual metric of biopharmaceutical innovation.
Clinical research is the most capital-intensive phase of drug development (Allred & Park, 2007;
Cockburn, 2011). Companies may be reluctant to enter this phase of development if they are not
confident that they would be able to recover that investment during the patent term of the
approved drug. In addition to the large capital investment need for clinical trials, this phase is
also the lengthiest period, often taking 7-9 years before final FDA approval (Scherer, 2007).
Therefore, the willingness of companies to invest the needed capital and time for clinical R&D
may be another strong indicator of the industry’s innovation in response to the BPCIA.

Like with any metric, there are limitations to using pre-clinical and/or clinical R&D
expenditures to measure innovation. There may be factors other than a policy change that can
influence a firm’s willingness to invest in R&D. For example, the general economic conditions
may affect a company’s ability or willingness to invest in research or certain technical
requirements may hinder its ability to develop a drug (even to explore a candidate molecule in
pre-clinical research). Appropriate controls must be used to isolate the direct influence of the
milestone event on the indicator of R&D. These controls may include overall (i.e., within
biopharmaceuticals and across different industries) R&D changes during the same time intervals, R&D levels for non-biopharmaceutical products, and governmental or academic research and development.

Another metric of the biopharmaceutical industry’s innovation may be the number of applications for biologic drug patents. The patent application is submitted once a potential new drug has been discovered and isolated, whereby the company protects the intellectual property rights to their research activities early in the process of drug discovery. While the BPCIA provides for 12 years of market exclusivity, patenting still stands as a legal tool for the protection of intellectual property. Future research can use the number of biopharmaceutical patent applications as a strong indicator of innovation levels by biopharmaceutical companies in response to the BPCIA.

The controls used to isolate the effect of patent policy change (i.e., milestones) on the indicator (i.e., the number of pharmaceutical patent applications on novel products) may include the number of non-biopharmaceutical patent applications during the same time interval, the awarding of noncommercial governmental and academic patents and the number of patents on products that did not enter clinical trials because of their low prospects of either scientific value or commercial success.

The flow of private capital (as opposed to public funds) into the biopharmaceutical industry also can be measured to gauge innovation activity within this sector. Because investment capital is attracted to sectors of the economy with high potential for return on investment, when capital flows into the pharmaceutical sector, it may indicate that investors have confidence in the sector’s ability to produce returns. Since biopharmaceutical companies make
profits from selling their drugs, their ability to make a profit often depends on intellectual property and market exclusivity for biopharmaceutical they have developed. The stronger (or longer) their exclusivity, the higher their potential to recoup their initial investment and make a profit (Pugatch et al., 2012).

Researchers may include an analysis of the dollar amount of private capital invested as a metric of innovation by biopharmaceutical companies. The willingness of institutional and individual investors to commit capital may be a significant indicator of the industry’s response to the BPCIA.

Some limitations to using the flow of private capital as an indicator of innovation must be considered. For example, the amount of capital invested into the biopharmaceutical industry may be skewed by the overall health of the economy. Additionally, as investors choose between available outlets for capital investment, the factors that determine their choices are influenced by many factors within capital markets (e.g., risks associated with equity purchases, the perception of the safety of the markets as a whole). Controls must be used to isolate the flow of private capital into the biopharmaceutical industry from conditions unrelated to the BPCIA include such as the total amount of private capital flowing into all sectors of the economy.


ARIAD PHARMS., INC. v. ELI LILLY & CO., 598 F.3d 1336 (Fed. Cir. 2010) (en banc); UNIV. OF ROCHESTER v. G.D. SEARLE & CO., 358 F.3d 916, 923 (Fed. Cir. 2004).


References Consulted


## APPENDIX

### Appendix 1: Clinical Trials Data Sets

Table 3. Federally funded phase 2 and 3 clinical trials for biologics registered in the FDA database between 2002 and 2016.

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Source: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
**Table 4.** Industry-funded phase 2 and 3 clinical trials for biologics registered in the FDA database between 2002 and 2016.

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Source: http://www.clinicaltrials.gov
**Table 5.** Institutionally funded phase 2 and 3 clinical trials for biologics registered in the FDA database between 2002 and 2016.

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Source: [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Appendix 2: FDA Approvals Data Sets

**Table 6.** FDA approvals for biologics (BLA), small-molecule drugs (NDA) and generics (ANDA) registered in the FDA between 2003 and 2016

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Source: http://www.fda.gov
Appendix 3: FDA Approvals of Biologic License Applications

Table 7. FDA approvals for biologics (BLA) registered between 2003 and 2016

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Table 7. FDA approvals for biologics (BLA) registered between 2003 and 2016 (continued)

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Source: http://www.fda.gov
Appendix 4: Statistical Analysis for Indicator 1 – Industry-Funded Clinical Trials

A regression analysis demonstrates the effect of time on Indicator 1. The time series explains 47.3% of the variance in number of trials performed.

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A regression analysis demonstrates the effect of time on Indicator 1. The time series explains 47.3% of the variance in number of trials performed.

For every year elapsed, the number of industry-funded clinical trials increased by 24.61 trials. This finding is statistically significant (P-Value = 0.003).
Appendix 4: Statistical Analysis for Indicator 1 – Industry-Funded Clinical Trials

T Test Period 2 Versus Period 1

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T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 1 shows that industry-sponsored clinical trials increased from an average of 39 to 340 per year. This increase is statistically significant (P-Value = 0.000).

T Test Period 3 Versus Period 2

<table>
<thead>
<tr>
<th></th>
<th>Period 3</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>340,000</td>
<td>480,000</td>
</tr>
<tr>
<td>Variance</td>
<td>676,000</td>
<td>92,333</td>
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<tr>
<td>Observations</td>
<td>3,000</td>
<td>3,000</td>
</tr>
<tr>
<td>Pooled Variance</td>
<td>483,333</td>
<td></td>
</tr>
<tr>
<td>Hypothesized Mean</td>
<td>0,000</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>3,000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
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</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0,003</td>
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</tr>
<tr>
<td>t Critical one-tail</td>
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<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
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</tr>
<tr>
<td>t Critical two-tail</td>
<td>3.182</td>
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</table>

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Indicator 1 shows that industry-sponsored clinical trials increased from an average of 340 to 480 per year. This increase is statistically significant (P-Value = 0.006).

T Test Period 4 Versus Period 3

<table>
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<th></th>
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<th>Period 3</th>
</tr>
</thead>
<tbody>
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<td>Mean</td>
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<tr>
<td>Variance</td>
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<td>98,000</td>
</tr>
<tr>
<td>Observations</td>
<td>7,000</td>
<td>2,000</td>
</tr>
<tr>
<td>Pooled Variance</td>
<td>611,651</td>
<td></td>
</tr>
<tr>
<td>Hypothesized Mean</td>
<td>0,000</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>7,000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>-4.454</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0,001</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.895</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0,003</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.365</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Indicator 1 shows that industry-sponsored clinical trials decreased from an average of 480 to 392 per year. This decrease is statistically significant (P-Value = 0.003).
Appendix 5: Statistical Analysis for Control 1 – Federally Funded Clinical Trials

A regression analysis demonstrates the effect of time on Control 1. The time series explains 7.2% of the variance in number of trials performed.

For every year elapsed, the number of federally funded clinical trials decreased by 2.84 trials. This finding is not statistically significant (P-Value = 0.173).
Appendix 5: Statistical Analysis for Control 1 – Federally Funded Clinical Trials

T Test: Period 2 Versus Period 1

<table>
<thead>
<tr>
<th></th>
<th>Period 2</th>
<th>Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>162.333</td>
<td>95.000</td>
</tr>
<tr>
<td>Variance</td>
<td>100.333</td>
<td>427.000</td>
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<tr>
<td>Observations</td>
<td>3.000</td>
<td>3.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
<td>263.667</td>
<td></td>
</tr>
<tr>
<td>Hypothesized Mean</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>4.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>5.079</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>2.132</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.776</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Control 1 shows that federally sponsored clinical trials increased from an average of 95 to 162 per year. This increase is statistically significant (P-Value = 0.007).

T Test: Period 3 Versus Period 2

<table>
<thead>
<tr>
<th></th>
<th>Period 3</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>121.500</td>
<td>162.333</td>
</tr>
<tr>
<td>Variance</td>
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<td>427.000</td>
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<tr>
<td>Observations</td>
<td>2.000</td>
<td>3.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
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<td></td>
</tr>
<tr>
<td>Hypothesized Mean</td>
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<td></td>
</tr>
<tr>
<td>df</td>
<td>3.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>-3.420</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>2.353</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.042</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>3.182</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Control 1 shows that federally sponsored clinical trials decreased from an average of 162 to 122 per year. This decrease is statistically significant (P-Value = 0.042).

T Test: Period 4 Versus Period 3

<table>
<thead>
<tr>
<th></th>
<th>Period 4</th>
<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>84.143</td>
<td>121.500</td>
</tr>
<tr>
<td>Variance</td>
<td>222.143</td>
<td>312.500</td>
</tr>
<tr>
<td>Observations</td>
<td>7.000</td>
<td>2.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
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<td></td>
</tr>
<tr>
<td>Hypothesized Mean</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>df</td>
<td>7.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
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<td></td>
</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.895</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.019</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.365</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Control 1 shows that federally sponsored clinical trials decreased from an average of 122 to 84 per year. This decrease is statistically significant (P-Value = 0.019).
Appendix 6: Statistical Analysis for Indicator 2 – Institutionally Funded Clinical Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Total</th>
<th>Time</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>14</td>
<td>9</td>
<td>23</td>
<td>0</td>
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</tr>
<tr>
<td>2003</td>
<td>16</td>
<td>9</td>
<td>25</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2004</td>
<td>13</td>
<td>5</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2005</td>
<td>78</td>
<td>19</td>
<td>97</td>
<td>3</td>
<td>2</td>
</tr>
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<td>2006</td>
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<tr>
<td>2007</td>
<td>82</td>
<td>29</td>
<td>111</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>2008</td>
<td>120</td>
<td>35</td>
<td>155</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>2009</td>
<td>130</td>
<td>29</td>
<td>159</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>2010</td>
<td>116</td>
<td>25</td>
<td>141</td>
<td>8</td>
<td>4</td>
</tr>
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<tr>
<td>2012</td>
<td>131</td>
<td>37</td>
<td>168</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>2013</td>
<td>128</td>
<td>33</td>
<td>161</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>2014</td>
<td>169</td>
<td>36</td>
<td>205</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>2015</td>
<td>184</td>
<td>52</td>
<td>236</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>2016</td>
<td>225</td>
<td>39</td>
<td>264</td>
<td>14</td>
<td>4</td>
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</tbody>
</table>

A regression analysis demonstrates the effect of time on Indicator 3. The time series explains 90.6 percent of the variance in number of trials performed.

For every year elapsed, the number of institutionally funded clinical trials decreased by 15.84 trials. This finding is statistically significant (P-Value = 0.000).
Appendix 6: Statistical Analysis for Indicator 2 – Institutionally Funded Clinical Trials

### T Test: Period 2 Versus Period 1

<table>
<thead>
<tr>
<th></th>
<th>Period 2</th>
<th>Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>99.667</td>
<td>22.000</td>
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<tr>
<td>Variance</td>
<td>105.333</td>
<td>13.000</td>
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<td>Observations</td>
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<td>3.000</td>
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<tr>
<td>Pooled Variance</td>
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<td>Hypothesized Mean</td>
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<td>df</td>
<td>4.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
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</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>2.132</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.776</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 2 shows that institutionally sponsored clinical trials increased from an average of 22 to 100 per year. This increase is statistically significant (P-Value = 0.000).

### T Test: Period 3 Versus Period 2

<table>
<thead>
<tr>
<th></th>
<th>Period 3</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>157.000</td>
<td>99.667</td>
</tr>
<tr>
<td>Variance</td>
<td>8.000</td>
<td>105.333</td>
</tr>
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<td>Observations</td>
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<td>3.000</td>
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<tr>
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<td>Hypothesized Mean</td>
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<td>df</td>
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</tr>
<tr>
<td>t Stat</td>
<td>7.356</td>
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<tr>
<td>P(T&lt;=t) one-tail</td>
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<tr>
<td>t Critical one-tail</td>
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</tr>
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<td>P(T&lt;=t) two-tail</td>
<td>0.005</td>
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</tr>
<tr>
<td>t Critical two-tail</td>
<td>3.182</td>
<td></td>
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</table>

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 2 shows that institutionally sponsored clinical trials increased from an average of 100 to 157 per year. This increase is statistically significant (P-Value = 0.005).

### T Test: Period 4 Versus Period 3

<table>
<thead>
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<th></th>
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<th>Period 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
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<td>157.000</td>
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</tr>
<tr>
<td>Observations</td>
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<tr>
<td>Pooled Variance</td>
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<tr>
<td>Hypothesized Mean</td>
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<td>df</td>
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</tr>
<tr>
<td>t Stat</td>
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<td>P(T&lt;=t) one-tail</td>
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</tr>
<tr>
<td>t Critical one-tail</td>
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</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.390</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.365</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 3 and post-Milestone 3 numbers for Indicator 2 shows that institutionally sponsored clinical trials increased from an average of 157 to 189 per year. This increase is not statistically significant (P-Value = 0.390).
Appendix 7: Statistical Analysis for Indicator 3 – FDA Approvals of BLAs

A regression analysis demonstrates the effect of time on Indicator 3. The time series explains 64.2% of the variance in number of approved BLAs.

For every year elapsed, the number of BLA approvals increased by 0.75. This finding is statistically significant (P-Value = 0.000).
Appendix 7: Statistical Analysis for Indicator 3 – FDA Approvals of BLAs

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Indicator 3 shows that FDA approvals of BLAs increased from an average of 3 to 6.8 per year. This increase is statistically significant (P-Value = 0.000).

<table>
<thead>
<tr>
<th></th>
<th>Period 2</th>
<th>Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
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<td>Variance</td>
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<td>0.800</td>
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<tr>
<td>Observations</td>
<td>4.000</td>
<td>6.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
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<tr>
<td>Hypothesized Mean</td>
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</tr>
<tr>
<td>df</td>
<td>8.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>7.539</td>
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</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.000</td>
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</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.860</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.306</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Indicator 3 shows that FDA approvals of BLAs increased from an average of 6.8 to 9.7 per year. This increase is not statistically significant (P-Value = 0.295).

<table>
<thead>
<tr>
<th></th>
<th>Period 3</th>
<th>Period 2</th>
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</thead>
<tbody>
<tr>
<td>Mean</td>
<td>9.667</td>
<td>6.750</td>
</tr>
<tr>
<td>Variance</td>
<td>26.333</td>
<td>0.250</td>
</tr>
<tr>
<td>Observations</td>
<td>3.000</td>
<td>4.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
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</tr>
<tr>
<td>Hypothesized Mean</td>
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<td></td>
</tr>
<tr>
<td>df</td>
<td>5.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
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</tr>
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</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.295</td>
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</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.571</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 8: Statistical Analysis for Control 2 – FDA Approvals of NDAs

A regression analysis demonstrates the effect of time on Control 2. The time series explains 40.4% of the variance in number of approved NDAs.

For every year elapsed, the number of NDA approvals increased by 1.91. This finding is statistically significant (P-Value = 0.009).
Appendix 8: Statistical Analysis for Control 2 – FDA Approvals of NDAs

T-Test performed to compare pre-Milestone 1 and post-Milestone 1 numbers for Control 2 shows that FDA approvals of NDAs increased from an average of 44.8 to 47.5 per year. This increase is not statistically significant (P-Value = 0.562).

<table>
<thead>
<tr>
<th></th>
<th>Period 2</th>
<th>Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
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<td>44.833</td>
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<tr>
<td>Variance</td>
<td>67.000</td>
<td>34.567</td>
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<tr>
<td>Observations</td>
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<td>6.000</td>
</tr>
<tr>
<td>Pooled Variance</td>
<td>46.729</td>
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</tr>
<tr>
<td>Hypothesized Mean</td>
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<td></td>
</tr>
<tr>
<td>df</td>
<td>8.000</td>
<td></td>
</tr>
<tr>
<td>t Stat</td>
<td>0.604</td>
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</tr>
<tr>
<td>P(T&lt;=t) one-tail</td>
<td>0.281</td>
<td></td>
</tr>
<tr>
<td>t Critical one-tail</td>
<td>1.860</td>
<td></td>
</tr>
<tr>
<td>P(T&lt;=t) two-tail</td>
<td>0.562</td>
<td></td>
</tr>
<tr>
<td>t Critical two-tail</td>
<td>2.306</td>
<td></td>
</tr>
</tbody>
</table>

T-Test performed to compare pre-Milestone 2 and post-Milestone 2 numbers for Control 2 shows that FDA approvals of NDAs increased from an average of 47.5 to 68.7 per year. This increase is not statistically significant (P-Value = 0.030).

<table>
<thead>
<tr>
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<th>Period 3</th>
<th>Period 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
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Appendix 9: Glossary

**Abbreviated New Drug Application (ANDA):** contains data submitted to FDA’s Center for Drug Evaluation and Research, Office of Generic Drugs, that provides for the review and approval of a generic drug. These generic drug applications are ‘abbreviated’ because they are generally do not require preclinical (i.e., animal) and clinical (i.e., human) data to establish safety and efficacy. However, a generic applicant must scientifically demonstrate that the product is bioequivalent (i.e., performs in the same manner as the innovator drug). Once approved, the generic may be manufactured and marketed to the American public as a safe, effective and low-cost alternative.

**Abbreviated New Drug Application (ANDA) Number:** a six-digit number assigned by the FDA to each application to market a generic drug in the United States.

**Active Ingredient:** any component that provides a pharmacological activity or other direct effects in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function in humans or animals.

**Approval History:** a chronological list of all FDA actions involving a drug product having a particular FDA application number (e.g., NDA, BLA or ANDA). There are more than 50 types of approval actions (e.g., changes in the labeling, new route of administration, and a new target patient population for a drug product).

**Biologic License Application (BLA):** biological products approved for marketing under the provisions of the Public Health Service (PHS) Act. The Act requires the manufacture of a biologic for sale in interstate commerce to hold a license for the product. A biologics license
application is a submission that contains specific information on the manufacturing processes, chemistry, pharmacology, clinical pharmacology and the medical effects of the biologic product.

**Biological Product:** include a wide range of products such as vaccines, blood and blood components, allergens, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from humans, animals or microorganism and may be produced by biotechnology. Gene-based and cellular biologics may be used to treat a variety of medical conditions for which no other treatments are available. In general, the term ‘drugs’ includes therapeutic biological products.

**Brand Name Drug:** a drug marketed under a proprietary, trademark-protected name.

**Dosage Form:** the physical form in which a drug is produced and dispensed (e.g., a tablet, a capsule or an injectable.

**Drug:** 1) a substance recognized by an official pharmacopoeia or formulary; 2) a substance intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease; 3) a substance (other than food) intended to affect the structure or any function of the body; 4) a substance intended for use as a component of a medicine (but not a device or a component, part or accessory of a device); 5) biological products are included within this definition and are generally covered by the same laws and regulations, but differences exist regarding their manufacturing processes (chemical process versus biological process.)
**Drug Product:** the finished dosage form that contains a drug substance (often, but not necessarily, in association with other inactive or active ingredients).

**FDA Action Date:** indicates when an FDA regulatory action, such as an original or supplemental approval, took place.

**FDA Application Number:** a unique number assigned to each application to market a drug in the United States. The types of application numbers are: NDA (New Drug Application), ANDA (Abbreviated New Drug Application) and Biologic License Application (BLA). A drug may have more than one application number if it has different dosage forms or routes of administration.

**Generic Drug:** the same compound as a brand name drug in dosage, safety, strength, how it is taken, quality, performance and intended use. Before approving a generic drug product, the FDA requires tests to assure that the generic drug can be substituted for the brand name drug. The FDA bases evaluations of substitutability (i.e., therapeutic equivalence) of generic drugs on scientific evaluations. A generic drug product must contain the identical amounts of the same active ingredient(s) as the brand name product. Drug products that are therapeutically equivalent have the same effect when substituted for the brand name product.

**Investigational New Drug (IND):** a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans.

**Label:** the official description of a drug product which includes an indication (i.e., what the drug is used for); target population; adverse events (i.e., side effects); instructions for uses by a
pregnant woman, children and other populations; and safety information for the patient. Labels are included with the packaging of the drug product.

**New Drug Application (NDA):** the sponsor submits evidence to the FDA on the drug’s safety and effectiveness for marketing approval. The application must contain data from specific technical viewpoints for review (i.e., chemistry, pharmacology, medical, biopharmaceutics and statistics). All NDAs are assigned an NDA number. Once the NDA is approved is approved, the product may be marketed in the United States.

**New Drug Application (NDA) Number:** a six-digit number the FDA assigns to each application to market a new drug in the United States. A drug can have more than one application number if it has different dosage forms or routes of administration.

**New Molecular Entity (NME):** an active ingredient that has never been marketed in the United States in any form. The NME is an active ingredient that contains no active moiety that has been previously approved in an application submitted under Section 505 of the Federal Food, Drug, and Cosmetic Act or has been previously marketed as a drug in the United States.

**Over-the-Counter Drugs (OTC):** drugs considered as safe and effective for use by the general public without a doctor’s prescription.

**Prescription Drug Product:** requires a doctor’s authorization to purchase.

**Product Number:** assigned to each drug product associated with an NDA (New Drug Application), ANDA (Abbreviated New Drug Application) and Biologic License Application (BLA). If a drug is available in different dosages, there are multiple product numbers.
**Review**: a comprehensive analysis of clinical trial data and other information prepared by FDA drug application reviewers. The review is divided into sections on a medical analysis, chemistry, clinical pharmacology, biopharmaceutics, pharmacology, statistics and microbiology.

**Review Priority**: describes New Drug Applications (NDAs) upon initial receipt and throughout the review process and to prioritize their review.

**RLD (Reference Listed Drug)**: an approved drug product to which new generic versions are compared to demonstrate that they are bioequivalent. A drug company seeking approval to market a generic equivalent must refer to the Reference Listed Drug in its Abbreviated New Drug Application (ANDA). By designating a single reference listed drug as the standard to which all generic versions must bioequivalent, the FDA attempts to avoid significant variations among generic drugs and their brand name counterpart.

**Route**: a way of administering a drug to a patient.

**Strength**: quantifies the amount of the active ingredient present in each dosage.

**Supplement**: an application to allow a company to make changes in a product that already has an approved drug application. Important drug application changes (e.g., packaging or ingredients) must be approved to ensure the conditions originally set for the product are still met.

**Submission**: grouping of supporting documents relative to an application. A submission belongs to only one specific application. There must be at least one submission for each application.

**Submission Classification**: provides a method to categorize new drug applications (NDA). The Submission Classification Code is assigned as a “Type” code (e.g., ‘Type 1’ is for a New
molecular entity (NME)). For Supplements, it describes the change to an FDA approved the application (e.g., a change in labeling, efficacy, dosage form or new indication).

**Summary Review**: a final decision whether or not to approve an application.

**Tentative Approval**: approval of a generic drug before the expiration of patents for the reference listed drug. The tentative approval details the terms. FDA delays final approval of the generic drug product until all patents or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

**Therapeutic Biological Product**: a protein derived from living material (e.g., cells or tissues) used to treat or cure disease.

**Therapeutic Equivalence (TE)**: pharmaceuticals that produce the same clinical effect and safety as the prescribed product. Therapeutically equivalent drugs must: have the same dosage form, be pharmaceutical equivalents with the same active ingredient, use the same route of administration; and have the same potency. The FDA designates a brand name drug or a generic drug to be the Reference Listed Drug (RLD) and assigns therapeutic equivalence codes based on data submitted in an ANDA. The manufacturer must scientifically demonstrate that its product is bioequivalent (i.e., the same effect as the Reference Listed Drug).

**Therapeutic Equivalence (TE) Codes**: designates whether the FDA has evaluated a particular approved product as therapeutically equivalent to other pharmaceutically equivalent products. Over-the-counter (OTC) drugs are not assigned TE codes. FDA assigns therapeutic equivalence codes to pharmaceutically equivalent drug products. A drug product is deemed to
be therapeutically equivalent based on scientific evidence establishing through *in vivo* or *in vitro* studies the bioequivalence of the product to a selected reference listed drug.