ABSTRACT

GUMMULURI, SREEDEVI. Drug Research and Development Incentives Under a Changing Exclusivity Environment: An Event Study Approach. (Under the direction of Stephen E. Margolis and Charles R. Knoeber).

In this dissertation I explore the effect of marginal changes in the exclusivity environment on research incentives of firms involved in the process of drug manufacturing, and drug research and development. A model of copyright developed by Landes and Posner (2003) explaining the effect of varying levels of copyright protection on research incentives, is closely followed here and adopted in a patent and regulatory context. Exclusivity here is taken to refer to the intellectual property environment and the regulations of the Food and Drug Administration (FDA) pertaining to marketing exclusivity for approved drugs. Both these aspects determine the period of time that drugs get marketed exclusively with limited competition and the amount that markets enable them to appropriate in return for their research activity. Intellectual property debates regarding the scope of patents and determination of patentable subject matter would inadvertently affect research intensive of firms such as pharmaceutical and biotechnology firms. Besides obtaining patents, drug marketing also has to go through a long process of approval from the FDA governed by the Federal Food Drug and Cosmetic Act (FFDCA). The Hatch-Waxman Act of 1984 brought about some crucial amendments to the drug regulatory process by enabling easy entry to generic drug manufacturers. Since the passage of the Hatch-Waxman Act, to the amendments introduced to the Hatch-Waxman Act through the Medicare Prescription Drug Act (2003), various court decisions have been instrumental in recognizing the weak links in the Hatch-Waxman amendments to the FFDCA (1938). These cases were precursors to some of the eventual statutory amendments to the Hatch-Waxman Act which were passed through the

Medicare Prescription Drug Act of 2003. In the current study, the reaction of three sets of firms- pharmaceuticals, biotechnology and generics drug manufacturers, are analyzed following some precedent-setting cases that changed the exclusivity available to new drugs entering the market. The event study methodology is used in evaluating their reaction to these changes. The study further determines whether these firms are affected consistently and significantly negatively or positively from these changes in exclusivity. As an extension to this study, the research behavior of pharmaceutical and biotechnology firms are also analyzed taking into account the abnormal returns obtained from these event studies.

DRUG RESEARCH AND DEVELOPMENT INCENTIVES UNDER A CHANGING EXCLUSIVITY ENVIRONMENT: AN EVENT STUDY APPPROACH

by

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BIOGRAPHY

Sreedevi Gummuluri was born in Bombay, India on the 28th of September 1979 to Dr. Eswara Prasad Gummuluri and Srikantha Gummuluri. She obtained her Bachelor's degree in Commerce from S.I.E.S college of Arts, Science and Commerce, Bombay on April 1999. While pursuing her Bachelor's degree she developed an interest in economics and decided to enroll into the Master's of Arts program in Economics at Bombay University, Kalina. Upon graduation with a Masters' degree in Economics from Bombay University, she further pursued her interest in the field by joining the PhD program in Economics at the North Carolina State University in fall 2001.

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CHAPTER 1

Introduction and Literature Review

Intellectual property came into existence as a means of providing exclusive rights to address the issue of appropriability. While easy imitation enables improved consumer welfare, it simultaneously acts as a disincentive for research. Patent law tries to balance these two conflicting objectives. Studies on different industries have demonstrated differing relevance of patents in each of them (See Levin et al., 1987 and Cohen et al., 1997). Cohen et al., (1997) use a questionnaire method to identify what a cross section of firms in different industries perceived as important in appropriating the benefits of research. Levin et al., (1987) use metrics such as lead time, secrecy, learning curve advantages, sales and service advantages and patents. In these studies pharmaceutical companies placed a higher importance on product and process patents in comparison with other industries such as software and semiconductors that placed more importance on lead time and learning curve advantages in appropriating benefits of new products and processes. The authors argue that in comparison with other industries, drug manufacturing companies can adopt clearer standards in assessing patent validity as patents are given out on unique compounds or chemical molecules. This enables clearer property creation and appropriation of research benefits. Grabowski and Vernon (1987) using sensitivity analysis tried to evaluate how sensitive innovation rates were to different rates of penetration by producers of imitative drugs into their market. Their finding was that a penetration rate from 10 percent to 50 percent significantly reduces returns to research and development and so reduces investment in these efforts. They further

establish that modest restoration in patent life for new drugs can have the effect of restoring reduced innovation and revenue

Drug development and marketing also faces considerable regulation in the United States. A unique character of the drug manufacturing industry is that many of these regulatory provisions can have the effect of controlling the marketing exclusivity of a drug. Approval by the Food and Drug Administration (FDA) to market a drug in the U.S. is just as important as obtaining a patent for drug companies to earn their revenues from research activity. Ramanathan (1999) showed in his study that for a portfolio of pharmaceutical firms, FDA approval of a drug mattered significantly in their value creation. It would follow then that any changes in regulations that affect the functioning of this approval process or ease the entry firms manufacturing imitation drugs may consequently affect drug research.

The drug manufacturing industry is characterized by heavy expenditure in research and development. DiMasi, Hansen and Grabowski (2003) have quoted this cost to be about $802 million in the discovery and development of a new drug. In addition it takes nearly 12 years for the investment period from initial drug synthesis to FDA approval which in-turn causes a reduction in the effective patent life available to market the drug. Drug research companies also tend to plow back their earnings into research. The Pharmaceutical Research and Manufacturers of America, PHRMA, estimate the domestic R&D expenditure as a percentage of domestic sales for this industry as 19.2 percent for 2005[1]. After the expiry of the patent on a drug, the cost of imitating it tends to

[1] Pharmaceutical Industry profile 2006 (Washington, DC: PhRMA, March 2006); Link: http://www.phrma.org/files/2006%20Industry%20Profile.pdf

be very low in this industry. Passage of the Hatch-Waxman Act[2], further eased the process of entry of firms producing imitation drugs. All these points make a case for offering protection on drug marketing to provide an incentive for drug research.

In essence, exclusivity in the form of patents and regulatory conditions are of consequence to drug companies in appropriating revenues from research. In this study the term exclusivity is used to refer to both the patent and regulatory condition faced by drug companies. While increasing exclusivity may impose social costs by delaying introduction of cheap drugs, they may be beneficial in recuperating research costs and encouraging research. Decreasing exclusivity on drugs on the other hand, may increase social benefits by easing entry of generics and imitators but would be expensive in the long run due to reduced availability of new and improved drugs. An economic issue worth investigating following this discussion is to what extent changes in exclusivity at the margin effect the research decisions of drug research and development companies. This is the motivation of the current study. The approach adopted is to study marginal changes in exclusivity provisions through legal changes and evaluating the effect of these changes on the research behavior of firms involved in drug research and development. This analysis is conducted using the event study methodology. In the current study, the drug research firms are considered to comprise firms in the pharmaceutical industry as well as biotechnology firms.

Various studies have investigated the relations that exist between patenting activity and R&D undertaken by research intensive firms using patent count data. Griliches (1981) conducts a time series cross-sectional analysis on large U.S. firms and finds that a significant relationship exists between the market value of firms, their R&D

[2] The Hatch-Waxman Act is discussed in more detail later in the chapter.

and number of patents. The market value of firms was computed here as the sum of equity and debt. He also found a significant independent effect of patent count on the market value of firms. Pakes (1985) analyzed stock market returns in noting that for large manufacturing firms, fluctuations in their market values are related to successful patent applications. She uses successful patent applications as a measure of the successful research and development activity of the firm. In a later paper Griliches, Hall and Pakes (1988) note that in the pharmaceutical industry there is evidence to suggest that patenting activity explains changes in the firm's market value measured in terms of stock market rate of return. Austin (2000) analyzed the value of patents as intangible assets to biotechnology firms applying the event study methodology based on the date of a patent grant. He uses patent statistics as a means of improving the estimates of R&D productivity change. In this study he finds significant changes in the market value of 20 biotechnology firms following a patent award especially in highly contested research areas. He also studies extensively if any spillovers are generated by patent awards in the form of economic benefits accruing to other firms in the industry not limited to knowledge spillovers. According to his model, a new patent could raise costs by narrowing research avenues or inducing infringement suits but at the same time a patent discloses knowledge that might complement a rival's research. Through empirical analysis he finds that new patents induce significant reevaluations to a patentee and his competitor's market value. New patents generated net spillovers valued from $2 to $4 million per patent per rival, indicating how R&D productivity could be mutually beneficial.

Various regulatory and statutory reforms aimed at the functioning of the drug industry have also been instrumental in the development of this industry over the years. Since the formation of the Food and Drug Administration (FDA) in 1938, various important reforms have followed such as the 1962 amendments to the Food, Drugs and Cosmetic Act, the Hatch-Waxman Act passed in 1984 and the Medicare Prescription Drug Act (2003). Peltzman (1973), in his evaluation of the 1962 amendments to the Food, Drugs and Cosmetic Act, noted that following these amendments there was a marked increase in compliance costs faced by drug developing firms which led to a reduction in drug innovation. Grabowski (1982) and Grabowski and Vernon (1983) came to a similar conclusion in their analysis noting that increased pre-marketing testing that followed this regulation was socially undesirable. The Hatch-Waxman Act passed in 1984 led to another important reform in the industry which enabled easy entry to generic drug makers producing imitative drugs while allowing an extension on market exclusivity to patent holding research firms. Studies on the effect of the Hatch-Waxman Act appear in general to indicate no net gain or loss to drug research intensive firms. Grabowski and Vernon (1986) compared revenues lost from generic entry to benefit accrued from patent extension and conclude that the effect would be a close trade off. Proctor (1989) used the event study methodology to show that the stock market expected the patent-term restoration law to have a positive financial effect on research-based pharmaceuticals. Joglekar and Paterson (1986) show that although generics take over a large market share following these reforms, investment in R&D continues to be attractive. These studies show that regulating firms involved in drug development end up effecting their research decisions.

Fewer studies have attempted the use of precedent-setting court decisions relating to patenting and regulation of drugs, in analyzing the valuation and research incentives of firms involved in drug research and development. In the current study, I concentrate more specifically on the exclusivity environment since the passage of the Hatch-Waxman Act (1984) to the introduction of amendments to this Act in 2003 through the Medicare Prescription Drug Act. Precedent-setting court cases that are expected to affect exclusivity during this time span are used in analyzing how marginal changes in the exclusivity environment can impact market valuation of firms involved in extensive drug research and development. These changes in the valuation of firms are expected to be indicative of changes in research incentives to firms. In chapter 3 the study is extended by analyzing how R&D expenditures of these firms are impacted following changes in their valuation recognized as statistically significant. The event study method is adopted in analyzing these changes in market valuation of firms, following these court events.

Event studies on statutory and regulatory changes usually face the issue of pinning down the exact date when the news is received by the market. In the current study, usage of precedent- setting cases in conducting event studies have the advantage of a surprise element in the final hearing as courts tend to guard their decision till the actual hearing takes place. An event study may therefore capture the relevant reaction of research firms following decisions involving changes to exclusivity. Chapter 2 elaborates on the event study methodology and presents the results of event studies performed on selected sets of major firms involved in drug research and generic drug manufacturing firms. Decision dates on selected precedent setting cases are used as the relevant event day. Details on these selected cases are also provided in Chapter 2. The cases selected in

this analysis cover some of the important decisions following the passage of the Hatch-Waxman Act leading up to the statutes relevant to drug research that were incorporated into the Medicare Prescription Drug Act (2003). Chapter 3 further extends the analysis by evaluating the eventual impact on R&D of major drug research firms following the change in the exclusivity environment.

The following sections in the current chapter present further background on patents, their relevance in drug research, the drug development process faced by drug research firms and regulations that are relevant to the cases selected and analyzed in this study.

1.1 Background on patents

The United States Patent and Trademark Office (USPTO) has defined a patent for an invention as the grant of a property right to an inventor. This right involves a right to "exclude others from making, using, offering for sale, or selling" the invention in the United States or "importing" the invention into the United States. There are three types of patents:

1) Utility patents may be granted to anyone who invents or discovers any new and useful process, machine, article of manufacture, or composition of matter, or any new and useful improvement thereof;

2) Design patents may be granted to anyone who invents a new, original, and ornamental design for an article of manufacture; and

3) Plant patents may be granted to anyone who invents or discovers and asexually reproduces any distinct and new variety of plant.

To be protected by a utility patent, inventions are statutorily expected to fulfill three essential requirements of utility, novelty and non-obviousness.

Patent rights are awarded by the government for a limited time period. The theory behind formation of patent laws or other forms of intellectual property for that matter, suggests that a free market with no exclusive rights will lead to too little production of intellectual works relative to an efficient outcome due to the public goods nature of knowledge. If exclusive rights are not provided to the inventor, then others can free ride on the knowledge. This would lead to issues of appropriation from an invention as the inventor is not able to completely recuperate the benefits from his or her invention. This creates a disincentive to undertake research activities. Thus awarding patents to the producers of knowledge should enable us to move closer to an efficient outcome. Another argument that has developed however is that IP law could in some circumstances lead to increased transaction costs that outweigh these gains. Restricting the free reuse of knowledge imposes transaction costs. Further royalties elevate the price of using intellectual property above zero, imposing social welfare losses. Intellectual property debates usually address these trade-offs that exist between the "incentives" of and "access" to an invention.

Dam (1994) points out that while intellectual property deals with the primary problem of enabling a firm to recover its returns from investment in research, it also helps in improving efficiency by overcoming some secondary problems that may be created in the system. Grant of patent rights may lead to cost advantages that permit a patentee to

enjoy an economic rent. The possibility of accruing an economic rent may cause firms to engage in rent- seeking behavior which could end up being socially wasteful. Rent-seeking generally implies engaging in an activity or incurring expenses with the intention of extracting uncompensated value from others without a contribution to productivity. In the present context, firms may incur various expenses during the patenting process with the intention of obtaining rents. These costs include administrative costs, costs of using the court system and costs incurred in enforcing rights all of which could be socially wasteful. R&D expenses that are duplicative in nature in cases where firms are competing over patents are again socially wasteful. The patent law limits rent-seeking behavior by firstly, making everyone aware of the new patent and its scope so that R&D from other firms can be redirected. Secondly, public disclosure enables firms to cut their own costs or build upon the knowledge in furthering knowledge-enhancement. Thirdly, the requirement of novelty and non-obviousness enables the elimination of discoveries with low contributions.

Nelson and Merges (1990) argue that it is essential that the patent system encourages early invention since larger numbers of inventions from increased R&D, positively impact future productivity growth and well-being[3]. This makes it important for researchers to apply as soon as possible to avoid delay or loss of patent to a competitor. At the same time increased search costs also act as a hindrance to early invention and reduce productivity. Patent law can again help reduce search costs and favor rules of early invention. In US, the 'first to invent' rule is adopted whereby the first inventor who conceives and reduces the technology or invention to practice is granted a patent rather than the 'first to file' rule followed by many other countries, whereby the first to file a

[3] Following works of Scherer (1984) pgs 257-59, 270-285; Pakes and Griliches (1980) pgs 377-381.

patent application regardless of the date of actual invention is granted protection for that invention. The 'first to invent' rule enables an inventor to economize on search costs. If an invention is found to exist as part of prior art or is found with the patent registry then resources would not be wasted in pursuit of patenting the same invention. This enables an improvement in productivity. Also since the patent is not granted until the invention in complete, inventors are encouraged to convert their ideas to practice as soon as possible. There is also a "time bar" rule in place where by a patent will not be issued if applied for one year after commercial use or publication describing the inventions. These provisions encourage early application and knowledge disbursement.

To address the issue of monopoly profits arising from patent rights, the length and breadth of a patent are also controlled by law. The length of a patent is restricted to 20 years from the date of filing. The breadth of a patent is determined by doctrines like the doctrine of equivalents and the reverse doctrine of equivalents. The doctrine of equivalents finds a device infringing if it performs substantially the same function in substantially the same way to obtain the same result as provided in a patented device. Application of this doctrine enables a patent to enjoy a broader scope. The reverse doctrine of equivalents on the other hand, has a narrowing effect on the scope of a patent. This is because a patent can be validly issued on a device if it performs a similar function as another device but in a substantially different way. Besides these doctrines there also exist patent misuse laws which form a branch of antitrust law and address concerns about a monopoly arising from patents.

Kitch (1977) points out that a patent system functions as a prospect system whereby the existence of a prospect and evidence of workability without any necessary

commercial value is sufficient for an inventor to apply for a patent. Following the logic of a prospect system, pioneer inventions may be given broad patent rights since it may be more efficient for a patent holder to invest in searching for commercial applicability of his or her inventions in comparison with other entrepreneurs who may have to rebuild whole new plants or reinvest in new projects to accomplish the same. The inventor could in this case contract more efficiently with complementary information bearers.

Merges and Nelson (1990) were however of the view that rivalry in invention is good since it encourages early invention. Landes and Posner (2003) point out that under some circumstances "depropertizing" intellectual property rights may be an economically sound policy. Rampant propertization of intellectual works could lead to a situation wherein it becomes difficult to find a substitute to the patented work subsequently conferring market power to the right holder. Creation of more patents may not necessarily equate increased innovation. Rent seeking becomes an essential cost to address. Following these arguments there would be a need to analyze the social cost justification of these rights.

The issue of patent length and breadth has been analyzed by Gilbert and Shapiro (1990) and Klemperer (1990). In a social context, narrow but long or broad but short patents were found to be socially optimal.

1.2 Relevance of patents in drug research

Merges and Nelson (1990) point to the importance of distinguishing among industries in studies of the impact of patent law on innovation, since technical advance doesn't proceed in the same manner in all industries. As per Nelson (1982) at least four

generic models are needed in characterizing inventive industries based on whether their inventions are representative of (1) a discrete invention (2) "cumulative" technologies, (3) chemical technologies (since chemicals technologies have their own characteristics), and (4) science- based technologies (where technical advance occurs outside the industry). These specifications are of particular importance when studying the patent scope issues. Discrete invention is characterized by invention that doesn't really point a way towards subsequent technical advances. The inputs and outputs usually stand alone and are not a part of integrated components or form a part of a bigger product. In industries such as automobiles, aircraft, software and semiconductor devices, invention is cumulative and builds on functions and features of existing technology. Unlike the case of cumulative technologies, broad patents for discrete inventions do not block inventions by other firms as much. In industries where innovation is cumulative- either sequential (successive inventions building on previous ones) or complementary (where potential innovators take different lines of research to enhance overall probability of innovation in a given time), competition and imitation may promote innovation[4]. For industries such as software or computers there is reason to believe that this holds true. Advances in the chemical industries on the other hand, are believed to have components of both discrete and cumulative inventions and some characteristics of their own as evident in the pharmaceutical industries. Unlike industries such as electronics and information technology, drug patents have received much support from the pharmaceutical industry for revenue creation to cover expensive drug development procedures for new drugs. Finally, science- based technologies include certain industries whose advance is driven

[4] Green and Scotchmer (1995), Jaffe (1986) and Henderson and Cockburn (1996)

predominantly by scientific developments as in the case of biotechnology. The inventions are very concentrated in certain areas and tend to be scientifically sophisticated. Over-broad patents in this area as in the case of pharmaceuticals can also be a hindrance to future advancement as per Merges and Nelson. They argue that once a scientific technique has been established, further innovation and application becomes more cumulative in nature. In such circumstances, allowing over-broad patents can end up making development of improvements much harder.

In the case of the pharmaceutical industry, the importance of patents has been demonstrated by many researchers. Edwin Mansfield in a 1988 study on 12 different industries showed that 65 percent of drugs would not have been introduced and 60 percent wouldn't have been developed had there been no patent protection[5]. Some other such studies, already discussed above, are Levin et al., (1987), Cohen et al., (1997) and Grabowski and Vernon (1987).

As Grabowski (2002) points out the importance of patents in the pharmaceutical industry is because of the characteristics of its R&D process. It takes several millions of dollars to discover, develop and gain regulatory approval for a new drug. Without patent protection, imitators could free ride on the innovative drug and duplicate the compound for a very small fraction of the costs that the innovative firm has to undertake. In that case drug research firms cannot completely appropriate the benefits from their innovation. Griliches and Cockburn (1994) note that revenue shares of a family of anti-infective drugs which went off patent in 1987 were halved in two years, following the entry of imitative drugs. Hughes, Moore and Snyder (2002) take a different approach by analyzing the change in consumer welfare from eliminating patent protection and an

[5] Mansfield (1988) pg 14

accelerated generic entry. The changes in consumer welfare are measured in the form of trade-offs between reduced costs of easily accessible medicines and the loss of health benefits from development of new drugs. They conclude that customers would lose roughly $3 in health benefits from future innovation for every $1 gained due to easier access to imitation drugs in the short term.

Similar results are also obtained in the biotechnology industry. Austin (1994) showed that there were significant stock market reactions when broad patents were issued in a data set consisting of 20 large biotechnology firms. The report also found that there is a positive correlation between stock price, when a patent is filed and issued, and research and development expenditure. In addition, he indicates that granting of an important patent appears to raise the net value of the entire industry.

In essence, firms involved in the manufacture and research of innovative pharmaceutical drugs or biological products are dependent on patents for appropriating their revenues. Grabowski and Vernon (1994) also point out that disproportionately large innovative contribution in the form of new drug introductions came from both new biotechnology firms and largest multinational pharmaceutical firms over the 1984 to 1989 period. This innovation process is also very dependent on the regulatory environment. The drug development process and the regulatory environment faced by the drug developing companies are further discussed in the following section.

1.3 Drug manufacturing industry background and regulation

The drug manufacturing industry has been a culmination of scientific advancement and regulatory changes over the past several decades[6]. Scientific

[6] See Daemmrich and Bowden (2005) for more on the emergence of the drug industry

advancements include both basic academic research and applied research which involves translating basic discoveries into commercial applications. Pharmaceutical chemicals first gained relevance in the drug research process with the advancement in testing synthetic organic chemicals in the process of creating medications. The world war eras especially saw significant experimentation and focus on synthesizing new drugs. Over these eras, many companies expanded in-house research and development projects while continuing to involve in basic research with academicians. Over the years many pharmaceutical companies have established themselves as essential drug research units and developed capabilities to mobilize resources essential in conducting large scale experimentation and testing of new drug compounds with the potential of curing ailments. Biotechnology started emerging as a contributor in drug development and disease prevention when the first recombinant DNA technologies were formulated in the seventies. It was around the early eighties that Genentech exploited this technology and obtained approval for the first biotechnology product, human insulin. Approval of man-made biological product patenting was also enabled in 1980 following an important Supreme Court ruling Diamond v. Chakrabarty[7]. Generic drug manufacturing also started gaining ground in the eighties after the passage of the Hatch-Waxman Act in 1984 which essentially eased the process of entry of these drugs. A generic drug is therapeutically equivalent (identical in strength, concentration and dosage form) to a brand-name patented drug and is generally made available when the patent on a brand-name drug expires. Generic drugs are usually not sold under a brand name and are referred to by the chemical make up of a drug. These drugs sell in markets that are subject to free entry and tend to be cheaper than brand-name drugs because of various cost advantages that they face. Unlike brand-name drug

[7] 447 U.S. 303

producers, generic drug manufacturers face lesser research and development costs, lesser costs of fulfillment of safety and efficacy requirements[8], and do not have to incur expensive marketing costs in disbursing information about the new drug's therapeutic effects.

In this study all three of these sectors, innovative pharmaceutical drug manufacturers, developers of biotechnological products, and generic drug manufacturers, are considered to comprise the drug manufacturing industry as a whole. However, it is only the pharmaceutical drug developers and developers of biotechnological products that usually engage in research and development activity with the intent of developing innovative drug products and patenting them. The Pharmaceutical Research and Manufacturers of America's (PhRMA) 2006 industry profile reports that the industry is estimated to have spent $51.3 billion on R&D in 2005. Domestic R&D as a percentage of domestic sales for this industry is estimated at 19.2 percent for 2005[9]. A PhRMA 2006 reports also found that about 418 new biotechnology medicines are in development dealing with over 100 diseases[10].

New drug research and development is a lengthy process involving a lot of risky investment by research firms. Not all research projects turn out fruitful. DiMasi (1995) points out that less than one percent of the compounds examined in the pre-clinical period make it to human testing and only 20 percent of the compounds entering clinical trials survive the developmental process and gain FDA approval. Grabowski and Vernon (2002) point out that returns on sales of drugs tend to be skewed with a few major drugs

[8] The safely and efficacy requirements are further discussed below
[9] Pharmaceutical Industry profile 2006 (Washington, DC: PhRMA, March 2006); Link: http://www.phrma.org/files/2006%20Industry%20Profile.pdf
[10] Pharmaceutical Research and Manufacturers of America report (Washington, DC: PhRMA, 2006); Link: http://www.phrma.org/files/Biotech%202006.pdf

producing rates of returns modestly covering the cost of capital. As per the study, in the nineties, 3 out of 10 marketed drugs ever produced revenues that matched or exceeded R&D costs. Much of the R&D expenditure is also attributed to the drug regulatory process faced by these firms. A 1998 Congressional Budget Office study indicates that an additional year of patent protection can increase the present value of returns to a typical pharmaceutical product by about $12 million, while a one-year acceleration of FDA review would yield an increase of $22 million[11]. Grabowski and Vernon (1986) also show a strong sensitivity of innovation levels to changes in regulatory clearance times. One-year reduction in regulatory review-time causes approximately 30 percent increase in industry revenues and R&D outlay. Some of the important regulatory amendments that have affected drug research and manufacturing are discussed below.

1.3.1 Kefauver - Harris amendments -1962

Regulation of pharmaceuticals in the US dates back to the early 1900's when the Food and Drugs Act 1906 was passed, aimed at prohibiting adulteration and setting up product labeling requirements to reveal ingredients used in a product. Institutionalization of safety regulation in the U.S. occurred with the passage of the Food, Drugs and Cosmetic Act of 1938. Following the passage of this Act, the Food and Drug Administration (FDA) was provided with increased authority in supervision of marketing new drugs including enabling it to request additional testing and authority to refuse allowance of marketing drugs that don't seem to conform to requirements. Clinically

[11] U.S. Congressional Budget Office report (July 1998)
Link: http://www.cbo.gov/showdoc.cfm?index=655&sequence=0&from=0#anchor

controlled trials for testing new drugs were increasingly promoted with the pharmaceutical industry maintaining responsibility in testing and sponsoring such trials.

Public and government scrutiny of pharmaceuticals was more pronounced since the 60's. Following the thalidomide tragedy, the 1962- Kefauver Harris amendments were introduced to the Food, Drugs and Cosmetic Act. The amendments provided guidelines on approved methods of clinical testing and provided the FDA with increased authority in approving and rejecting New Drug Applications (NDA). The main requirements of the amendments were to incorporate efficacy testing along with the safety tests in the new drug approval process.

The development of a drug goes through multiple phases before and after the drug actually gets launched[12]. This begins usually with basic scientific research often conducted by academic and medical institutions that are substantially funded by the NIH and other federal agencies. The pharmaceutical companies have been instrumental in conducting most applied research for converting basic research into commercial products relevant to clinical therapy. Many chemical compounds based on basic research are evaluated using laboratory and animal studies initially. These pre clinical tests have very low success rates and can take anywhere between 2 to 5 years. Once a viable drug emerges from this process of applied research it goes through a rigorous clinical research process regulated by the U.S. Food and Drug Administration. The FDA rules require tests that must demonstrate that the drug is both safe and efficacious. This involves 3 phases of trials.

[12] See Charles Phelps (2002) Chapter 15 pg 532

Phase 1-Initial safety tests- Phase one trials involve testing the drug on 20 to 100 healthy volunteers primarily to determine safety by administering absorption, metabolism, and toxicity. The probability of success at this stage is around 50-70%. This process takes between 1-2 years.

Phase 2- Initial efficacy testing- This phase involves administering the drug on 100-300 patients with the disease primarily to determine the efficacy of the drug. Of the drugs that pass phase 1 tests, the probability that they reach the next phase is around 50% taking between 2 to 5 years.

Phase 3- Extensive Efficacy and Safety testing- After initial efficacy tests extensive tests are undertaken on 300 to 3000 patients to provide a much larger sample to confirm efficacy. The probability of getting past this stage is usually much higher, around 75%. This stage takes around 2 to 3 years.

After this phase follows the post marketing surveillance in which doctors and pharmacists are required to submit to the FDA any adverse events associated with taking the drug. The FDA analyzes this data and sometimes withdraws a drug from the market on the basis of information from this stage.

The effect of the 1962 amendment was increased clinical testing, regulatory scrutiny of drugs and increased debate among the drug manufacturing community about lags in drug introduction. The regulation did have a positive effect on reducing the risk of endangering public health from ineffective, experimental drugs and drugs introduced without complete testing. Some studies like Peltzman (1973), Grabowski (1982) and

Grabowski and Vernon (1983) however noted that following these amendments there was a marked increase in pre-marketing testing and compliance costs faced by drug developing firms which led to a socially undesirable reduction in drug innovation.

1.3.2 Hatch-Waxman Act - 1984

Around the eighties rising pharmaceutical drug prices started developing as a policy issue. In 1984 Drug Price Competition and Patent Term Restoration Act was passed with the intent of addressing this issue. This Act is also called the Hatch-Waxman Act[13]. The Hatch-Waxman Act aimed at increasing competition in drug manufacturing by hastening the approval of generic drugs. It simultaneously made available a patent term restoration provision on approved new drugs that lose out on the benefits of patent protection due to the extended regulatory process. The Act was seen as an attempt at reconciling the incentives from pharmaceutical research with quicker access to cheap drugs. Passage of the Hatch-Waxman Act also briefly followed FDA's first publication of "Approved Drug Products with Therapeutic Equivalence Evaluations" also called the "Orange Book" in 1980. The Orange Book lists products that have been fully reviewed by the FDA for safety and efficacy and for which New Drug Applications (NDA) have been approved. Pursuant to the Hatch-Waxman Act the book also lists approved generic drug products along with information about patents on NDAs and periods of marketing exclusivity. Some of the main provisions of this act include a statutory exemption for patent infringement relating to regulatory marketing approval, patent term extension,

[13] Pub. L. No. 98-417, 98 Stat. 1585 (1984)

procedures for challenging the validity of pharmaceutical patents, and a reward for challenging the validity, enforceability, or infringement of a patented and approved drug.

One of the main purposes of the Hatch-Waxman Act was easing generic entry. This was done by allowing a new type of application for market approval of a generic drug. This application was called the Abbreviated New Drug Application (ANDA). An ANDA may be filed if the active ingredient of a generic drug is the bioequivalent (same active substance and dosage form) of an approved drug. An ANDA allows a generic drug manufacturer to rely upon the safety and efficacy testing of an approved NDA for its own approval. This has the advantage of forgoing all the development and clinical testing costs that an NDA had to go through in order to get approved. An approved ANDA gets listed on the Orange book and can proceed to marketing the drug as soon as the patent on the original drug expires.

The patent term restoration provision allows an extension to patents on drugs that lost a portion of the term to clinical testing procedures. The Act however places certain caps on the length of the term restoration. The patent term restored cannot exceed five years. Further, the remaining patent term post restoration cannot exceed 14 years.

The provisions on procedures for challenging the validity of pharmaceutical patents, and the rewards that ensue in case such a challenge is successful, were probably instrumental in leading to most suits between patent- holding firms and generics. Under the Hatch-Waxman Act, each holder of an approved NDA must list the relevant patents it believes would be infringed if a generic were marketed before its expiration. The FDA publishes this list in the “Orange Book”. The FDA oversees the listing of drugs on the Orange Book but maintains that it only plays a ministerial role and does not have the

expertise to check on the propriety of the listings. A company filing an ANDA must provide certification to the FDA about the specific patent associated with its generic drug. The Act provides four possibilities under which an ANDA can seek approval:

1. the patent information on the drug has not been filed;
2. the patent has already expired;
3. a date on which the patent will be expiring; or
4. the patent is invalid or will not be infringed by the manufacture, use or sale of the drug for which the ANDA is submitted.

These possibilities are referred to as the paragraph 1, 2, 3, and 4 certifications respectively. ANDA certifications under paragraph 1 or 2 are approved almost immediately after meeting all applicable regulatory and scientific requirements. An ANDA certified under paragraph 3 is required to wait for approval until the patent on listed drug expires even though all the pertinent regulatory and scientific requirements are met.

If a paragraph 4 certification is made, the company filing the ANDA is required to immediately notify the patent holding firm. The patent owner may then bring an infringement suit within forty-five days of receiving such a notification. If the patent owner files a timely infringement suit, then the FDA suspends approval of the ANDA until:

1. the date of the court's decision that the listed drug's patent is either invalid or not infringed; or
2. the date the listed drug's patent expires, if the court finds the listed drug's patent infringed; or

3. subject to modification by the court, the date that is thirty months from the date of the owner of the listed drug's patent received notice of the filing of a paragraph 4 certification.

The Act also rewards a generic drug manufacturer for challenging the patent associated with an approved pharmaceutical. It provides a 180-day exclusive marketing period to the first generic drug applicant to file a paragraph 4 certification. The intention of this provision is to reward the generic drug applicant for pointing out an incorrect listing that delays entry and to encourage generic drug makers to find and challenge such listings. This exclusivity period is triggered if one of two statutory conditions is met[14],

1. a court decision finding the patent to be invalid, unenforceable, or not infringed by the ANDA product; or
2. first commercial marketing of the ANDA product.

The first is sometimes referred to as the "court decision trigger" and the second is referred to as the "commercial marketing trigger".

After the passage of Hatch-Waxman Act however, various issues arose concerning the provisions of the Act. One such issue was highlighted by the decision in Mova v. Shalala[15] regarding circumstances under which the 180-day exclusivity period was available to the first generic drug applicant to file a paragraph four certification. The FDA interpreted this provision to mean that the first generic drug applicant was required to win the infringement suit in order to enjoy the exclusive marketing reward. The Court however decided that first generic drug applicant to file a paragraph four certification, was not required as per the plain language of the statute to "successfully defend" itself in

[14] Section 505 (j) (5) (B) (iv)
[15] 955 F. Supp. 128 (D.D.C. 1997), 140 F.3d 1060

order to be awarded the exclusivity period since such an interpretation would essentially have the effect of removing the 'first commercial marketing' provision of the 180-day exclusivity provision. It also stressed that the intention of the congress in making this provision may have been to reward the first generic applicant whether or not they were later sued which would not be the case under the FDA interpretation. Consequently, circumstances arose where generic drug manufacturers rushed to file paragraph 4 certifications in order to gain the first-to-file status so as to gain rights over the 180-day exclusivity provision. This enabled an increase in competition in the market prior to the expiry of the patent. The provision in general also met with a lot of criticism for causing sham paragraph four certifications by generic drug manufacturers intending to avail themselves of this reward[16].

Besides the "successful defense" provision of the FDA, the definition of a court decision under the "court decision trigger" (whether the result of a declaratory judgment action would be a valid decision, would this include a decision that is appealed etc) and the level of the decision (District Court or at the Federal Circuit level) that is deemed valid in claiming the 180-day exclusivity period were also issues of dispute.

Provisions of the Act also brought attention to improper Orange Book listings of patent holding firms. As noted previously, the FDA asserts that it plays only a ministerial role in over seeing the Orange Book listings and was ill- equipped in checking on the propriety of the listed claims. The Act also does not provide generic drug producers with sufficient channels to question a particular Orange Book listing or a procedure to delist a wrong listing. As per the provisions of the Act, a generic drug producer seeking to resolve the propriety of a listing could at the most make such a request to the FDA. The

[16] See Schacht and Thomas (2004) pg 4, Eisenberg (2001), Engelberg (1999) pg 389

FDA would in turn pass the request to the firm which filed the NDA and made the listing. If the NDA holding firm states that the listing is proper the FDA simply accepts such a statement and denies any firm submitting an ANDA from seeking approval on those listings.

The thirty month stay provision of the Act was also a cause of concern in circumstances where patent holding firms managed to make late listings on the Orange Book and file patent infringement suits against firms filing ANDAs seeking approval of their drugs. The FDA would then end up having to stall ANDA applications for at least thirty months till the issue is resolved. Some of the case law emerging from such circumstances is further discussed in Chapter two. Many of these cases were instrumental in shaping up the policies that got eventually incorporated into the provisions of The Medicare Prescription Drug Act (2003) that are relevant to the drug manufacturing industry[17].

1.3.3 Medicare Prescription Drug Act- 2003: Some relevant amendments to Hatch-Waxman Act 1984

The Medicare Prescription Drug Act (2003) introduced some relevant amendments to the Hatch-Waxman provisions. Firstly, new patent listing rules came into force. Permitted listings were to include patents on active ingredients, drug formulations and uses of a drug. Listings on drug packaging, metabolites and intermediate forms of a drug which were also leading to improper listing issues, were disallowed. Further, a detailed signed attestation accompanying a patent submission towards Orange Book

[17] Pub. L. No. 108-173, Title XI, 1101, 1102 (codified as amended at 21 U.S.C. 355(j) (2) and (5) (2004)).

listings were required and false statements could lead to criminal charges. This was done with the intention of improving disclosure requirements on relevant patent listings and controlling inappropriate listings. Secondly, only one 30-month stay was permitted for a patent listing that has been challenged so as to curb misuse of this provision and delaying entry of competitive drug producers. Thirdly, an ANDA applicant against whom a patent infringement suit has been filed may assert a counter claim to delist or delete patent information that has been wrongly submitted to the Orange Book hence providing an avenue to generic drug producers to contest a listing. Fourthly, generic drug applicants were also permitted to file a declaratory judgment action to obtain patent certainty if a patent infringement suit is not filed by an NDA within forty five days of notification.

With respect to the 180-day exclusivity provision, the Medicare Act amendments removed the "court decision trigger" altogether with the intension of encouraging early marketing of FDA- approved generic products and curtail any abuse of the provision. The new provisions focus on the "commercial marketing trigger" while imposing a time constraint on the first generic drug applicant to utilize this exclusivity period. As per the new provisions, the first company to file an ANDA must market its product within 75 days of final FDA approval or thirty months after submission of its ANDA, whichever is earlier. The exclusivity period commences 75 days after a decision of a court from which no appeal has been or will be taken. The generic applicant would not have to face the risk of losing a portion of its exclusivity period if it decided to wait till the appellate court's decision. The court decision or order may be the result of any applicant that has received tentative approval or in a declaratory judgment action brought by any company filing an ANDA against the patent owner.

The Medicare Act also applies the 180-day exclusive marketing provision on a product-by-product, as opposed to a patent-by-patent basis followed previously. The exclusivity period is allowed to be shared among all the applicants who file a paragraph four certification to any listed patent on the date the first paragraph-four certification is filed for a particular product. After that date, an applicant that is the first to file a paragraph-four certification to a different patent listed for the same product will not receive any exclusivity. This was expected to clarify the application of the 180-day exclusivity provision, curtail any frivolous lawsuits relating to that product and hasten entry of other generic drug manufacturers.

In effect, the Medicare Prescription Drug Act (2003) appears to have brought about some essential changes in the Hatch-Waxman Act provisions which may clear up some of the ambiguities created with regard to the exclusivity environment faced by drugs and help further ease up the process of generic drug entry to enhance competition and reduction in drug prices in the U.S.[18]

[18] See Derzko (2005) pg 165 for a comprehensive discussion on Medicare Prescription Drug Act's Hatch-Waxman provisions and its consequences.

CHAPTER 2

Analyzing the effect of changes in exclusivity using the event study method

2.1 Introduction and Research Question

Firms in research intensive lines of business argue about the importance of patents in encouraging innovation, the pharmaceutical and biotechnology industries being no exception. These industries are different from most other research intensive industries in that they not only face pressures from patent terms running out before recuperation of their research investment, but also face regulatory restrictions from the FDA in assuring that the products are safe and effective in usage. The FDA regulatory requirements also end up affecting the drug development times. Given these circumstances, it is not just the acquisition of a patent which is of consequence to profit-motivated firms but also the FDA's approval to market the drug. Such approved drugs along with the claims that related patents cover get listed on FDA's Approved Drug Products with Therapeutic Equivalence Evaluations or the "Orange Book". While the FDA maintains that it does not have the expertise to check on the propriety of patent claims being listed in the Orange Book and that's not a role it is expected to play, it does oversee the drug listing and its therapeutic features. The Hatch-Waxman Act (1984), which followed briefly after the first publication of Approved Drug Products by FDA in 1980, brought with it a whole new set of legal battles over improper listing of drugs on the Orange Book and "evergreening" patent claims in an attempt to extend protection. The Hatch-Waxman Act was known for enabling easier entry for generics into the drug market by allowing them to seek approval for their drugs without having to replicate the drug tests conducted by New Drug Applicants (NDA) as long as they showed that their drugs were similar in

composition to that of approved and listed drugs. Along with easy entry the Act also allowed for an extension in patent term to innovative firms as a compromise. The Act also had a provision for 180-day marketing exclusivity granted to the first generic to contest the validity of a listed drug. Various loopholes in the statutes emerged over a period of time leading to court battles. While the Medicare Prescription Drug Act (2003)[19] closes some of these loopholes, some precedent- setting cases have been instrumental in shaping the policies that were eventually incorporated into this Act.

From the above discussion it would follow that both the patent and the regulatory environments shape the market exclusivity that innovating firms face and the research investment decisions these firms make[20]. In this study, the patent and the regulatory environment are together referred to as the exclusivity environment faced by firms. The question of interest here is how do marginal changes in exclusivity affect the returns and incentives of drug manufacturing firms? In the case of research intensive firms, these changes in returns are considered to be representative of their research incentives. Marginal changes in exclusivity are taken to be reflected by changes in the patent and the regulatory environment. A compilation of precedent-setting cases are expected to have incited these marginal changes in exclusivity. Precedent-setting cases have the effect of changing rules that uniformly affect claims on exclusivity enjoyed by innovative firms. Cases which increase or expand this exclusivity might be viewed as encouraging by research firms. On the other hand, cases reducing or contracting this exclusivity may be viewed as discouraging to research.

[19] Pub. L. No. 108-173, Title XI, 1101, 1102 (codified as amended at 21 U.S.C. 355(j) (2) and (5) (2004)).
[20] Kannan Ramanathan in his study showed that FDA approval matters more than patent approval in value creation for many pharmaceuticals. Ramanathan (1999) pg 3437

In this chapter the method used to measure the effect of a change in exclusivity on drug manufacturing firms is illustrated, events or the cases of consequence are recognized and the effect of these events are evaluated. Measurement of the change in firm returns following these cases is done using the event study methodology. Not many studies have attempted to analyze the effect of patent cases using the event study methodology. Lunney (2005) makes such an attempt and in general finds evidence supporting the conception that there might be a causal relation between court decisions and observed stock price reactions for drug company portfolios[21]. The result of that study is encouraging for the current study which uses event studies to evaluate the effect of selected cases of interest to drug companies and further analyzes these effects based on a theoretical model in an attempt to determine the cause of an observed change.

2.2 Theoretical model

In order to analyze the effect of a change in exclusivity it can firstly be recognized that innovative firms face tradeoffs between their returns to innovation and the cost-of-innovating. Landes and Posner (2003)[22] developed a model of copyright illustrating this trade-off based on Salop and Scheffman's (1987) model on how dominant firms choose strategies that raise their own and their rival's costs. Patents and regulatory exclusivity can also be presented as following this relation. Changes in market exclusivity due to amendments to patent law and regulation may have the effect of changing the returns from the innovative activity of drug research and manufacturing firms while also changing the costs faced by all drug manufacturing firms including generic drug makers.

[21] Lunney (2005)
[22] See Landes and Posner (2003) pg 71-76.

A change in patent law allowing a broader scope to patents would on one hand enhance the returns appropriated by innovative drug producers, but on the other, would increase their cost of innovating by decreasing the available patentable research domain. At the same time, producers of competitive drugs would face higher costs of finding the means to penetrate the market. Similarly, a regulation that allows a patent holding firm to list a broad set of claims on the Orange Book or allows a late listing on a drug, would qualify a drug for an extended exclusive marketing period and stall entry of generic drug manufacturers. On one hand such a regulation would enhance the returns appropriated by patent holding firms, while on the other, their costs incurred in the process of innovation will increase as their expenses in finding new patentable claims along with the regulatory listing expenses will increase. Producers of competitive drugs would again face higher costs of finding means to penetrate the market.

Another possible circumstance is a regulation that eases the entry process of generic drug makers by allowing them an easy means to contest a patent listing or allowing quicker entry procedures such as, the allowance of filing for a paragraph-four certification and enjoying of the 180-day exclusive marketing period before the listed patents on a new drug expire. Such a regulation would possibly decrease returns of an innovative drug producer while also decreasing their costs of innovating as they would face lower costs of licensing and easily obtain substitutes to their research inputs. As the entry process is simplified, generic drug makers would also face a decreased cost of penetration as the available patentable research domain or the listable patent claims are altered and diminished.

In what follows, I closely adopt Landes and Posner's framework to analyze the effect of changes in exclusivity in the form of patents or regulations that effect drug innovation and drug marketing.

Some simplifying assumptions are made. A simple static framework with no uncertainty in demand is assumed. A set of firms are involved in developing new inventions with the intention of patenting them and converting them into finished products that are demanded by consumers in the market for drugs. These firms are referred to as the inventors. At the same time there exist firms that produce substitutes to the inventor's product. They do this by finding various means of working around the claims of patent owners. In drug markets this is one of the characteristics of generic drug manufacturing firms. They are involved in the business of manufacturing drugs that are equivalent to the drugs manufactured by inventing firms who sell their drugs under a brand name. Generic drugs are essentially copies of the branded drugs. Generic drugs can be legally sold in case 1) the patent has expired, 2) the generic company certifies the brand name company's patents are either invalid, unenforceable, or will not be infringed, 3) the drugs never held patents or if the firms invent around the existing patents, or 4) patent law is not in force as is the case in certain countries. In the U.S., passage of the Hatch-Waxman Act in 1984 brought about regulatory changes that eased the process of entry of generic drug makers into the drug production market. It also enabled early entry of generic drugs as they can avoid the safety and efficacy tests that patenting firms have to go through. It further included a paragraph-four certification clause which enables entry before patent expiration if the patents listed on the Orange Book were contested as being invalid, unenforceable or not infringed. In this model, generic drug manufacturing

firms are analogous to the copiers of copyrighted material considered in Landes and Posner's model.

The price of a drug is denoted by p, the market demand for a drug is represented by $q(p)$, x and y denote the quantity produced by the inventor and the substitute drug makers respectively so that, $x + y = q$. The marginal costs of production faced by the inventors are constant and denoted by c.

Production and demand structures are assumed similar across innovating firms. Cost of innovation is denoted by e. Cost of innovation here refers to the basic costs that go into the process of research, innovation, patent application process and marketing. This could include costs of setting up and running a research unit, licensing costs, transaction costs etc. The level of exclusivity is denoted by $z \geq 0$, so that $z = 0$ implies no protection or exclusivity and $z = 1$ signifies complete exclusivity. The index z is assumed to measure all the aspects of patent protection and exclusivity such as the current legal and statutory provisions with regards to infringement and exclusivity, the FDA regulatory environment, the elements and claims being protected, the duration of protection, and the efficacy and cost of enforcement.

Firms producing substitutes are like fringe firms in a dominant firm model, supplying substitutes to the point that their marginal cost equals price. Marginal cost of firms producing substitute drugs is assumed to increase as the production of drugs increases and as exclusivity provided to firms marketing the innovative drug increases. This is an essential assumption because if the marginal costs of substitute drug producing firms do not rise, then that would imply that inventions can be easily reproduced and there would be no incentive for innovators to innovate. From this assumption it follows

that an increase in exclusivity in the form of stronger patent protection or changes in regulation that enhance the exclusivity provided to firms marketing innovative drugs, increases the cost of producing substitutes. Also, at a given level of $z < 1$ some producers of substitutes may easily find the necessary resources in order to produce substitutes but some others may find it harder to produce substitutes. These differences in cost of providing substitutes, causes the supply curve of substitute drug producers to be upward sloping.

Supply of the substitute drug producer can be written as:

$$y = y(p, z) \tag{2.1}$$

with $y_p > 0$ and $y_z < 0$. $y_p > 0$ implies that an expectation of higher prices induces increased efforts among producers of substitutes to obtain certifications to market generics or to find means of producing non-infringing substitutes. As shown later in figure 2.1 this could be represented by an upward sloping curve. It essentially represents a locus of penetration by substitute producers as a function of the branded drug price. Branded drugs having entered the market first have the advantage of being established and creating a sense of brand confidence among users. Substitute drug producers would in effect have to incur substantial costs to be the first generic drug to enter the market so as to enjoy a brief 180-day period of exclusivity. Even without this 180-day exclusivity period substitute drug producers would have to incur substantial costs to enter a market where significant brand loyalty is established. Another reason to expect the supply curve to be upward sloping also has to do with the ease of market penetration. With an increase in branded drug price, greater attention is given to generic drug availability by doctors,

users, insurance programs, managed care programs etc which the generic drug manufacturers aim to fulfill.

The net returns of an innovator can be expressed as:

$$\Pi = (p - c)\, x - e(z) \tag{2.2}$$

and substituting for x equation 2.2 can be written as

$$\Pi = (p - c)\,[q(p) - y(p, z)] - e(z) \tag{2.3}$$

where, *e (z)* denotes the innovator's cost of innovation which is represented as a function of z, the index for exclusivity. The cost of innovation faced by innovative firms would be higher the greater the exclusivity. Changes in exclusivity from changes in patent and the regulatory environment considered here, have the affect of altering the research domain available to subsequent innovators or other costs in their research process. An increase in exclusivity due to a change in patentability for instance, would have the effect of decreasing available patentable domain. This in turn would increase the costs that firms have to incur in making new innovations, as their research efforts would have increased. Or with a regulatory change that enhances their exclusivity, they may have to incur increased licensing costs, transactions costs, bargaining costs, increased costs of finding a non-infringing substitutable input that can be used in innovative production or increased regulatory listing costs[23]. If we denote an innovator's gross profit by G, which would equal his revenue less the cost $(p - c)x$, the condition for innovation is given by,

$$G \geq e(z) \tag{2.4}$$

[23] Following Landes and Posner (2003) and Salop and Scheffman (1987), the assumption made here is that with an increase in exclusivity the inventor's face a higher fixed cost in the form on the cost-of-innovation while also raising the marginal costs of producers of substitutes as discussed above.

The market for drugs is shown in figure 2.1. The supply curve of producers of substitutes $y = y(p, z)$ is an upward sloping curve for reasons discussed above. The market demand is represented by the downward sloping *q(p)* curve. The demand curve for an innovator is obtained by subtracting the supply curve of producers of substitutes from the market demand. The figure shows that at price p^0, the innovator produces x^0 units while the producers of substitutes produce y^0 units. The total units produced are q^0 at p^0 (so that, $q^0 = x^0 + y^0$). The gross profit of the innovator is represented by the shaded area. Given this situation, following an expansion in exclusivity, which could mean strengthened patents or passage of regulations that enhance exclusivity provided to inventions of innovative firms, the supply curve of producers of substitutes will swing inwards as their cost of producing substitutes rise. In effect quantity produced by producers of substitutes decreases while that of innovators increases. The gross profits of innovating firms would also be enhanced as the price at which they sell along with the quantity they sell increase as shown in figure 2.3.

Turning next to the market of new innovations, let N denote the number of inventions of an innovative firm. The term *e(z)* is allowed to vary across innovating firms which implies that some firms would be more efficient at inventing and recognizing new areas of patentability or acquiring exclusive rights in comparison with others. Such firms would face lower costs of innovation than others. The number of inventions in the market for new inventions rise until the cost of innovation of the marginal patentee equals his gross profit *G*. The number of inventions that are created can therefore be represented as a function of *G* and *z* as shown in equation 2.5 below. The supply curve for new inventions is as shown in figure 2.2.

$$N = N(G, z),$$

where, $N_G > 0$ and $N_z < 0$ (2.5)

The net effect on N of an increase in exclusivity depends on two aspects. First, a movement up the supply curve following an increase in gross profits, as discussed above, and an upward shift in the supply curve as a consequence of increased costs of innovation faced by the innovators due to a decrease in research domain or an increase in regulatory listing costs. Some amount of exclusivity is essential because of the ease of reproducing the inventor's commodity. However an increase in exclusivity has a counter effect of increasing the cost of innovation that the inventor faces. The innovator's decision to produce new inventions hinges upon the net of these two effects. If the cost of innovation increases substantially, it may have the effect of decreasing the number of new works produced by inventors. Thus, $dN/dz = N_G(dG/dz) + N_z$. At low levels of z, the gross profits-enhancing effect of exclusivity would dominate, so that $dN/dz > 0$. When z is very low, free riding from producers of substitutes may prevent inventors from covering their costs of innovation and coming up with new inventions. An increase in z would then lead to an increase in *N*. This however occurs until some point say $\bar{z}$. Beyond $\bar{z}$ increases in the cost of innovation to marginal patentee will dominate so that the returns begin to fall. So, $dN/dz > 0$ for all $z < \bar{z}$, $dN/dz = 0$ at $\bar{z}$, and $dN/dz < 0$ for all $z > \bar{z}$. A similar but opposite situation would be faced in case of a reduction in exclusivity.

Diagrammatically, in figure 2.2, an increase in exclusivity leads to an increase in the number of inventions. At exclusivity level z^0, the equilibrium gross profits are represented by G^0 from figure 2.1 and supply curve $N = N(G, z^0)$. If there is an expansion in exclusivity, the gross profits shift up to G^1 but at the same time the supply curve shifts

inward to $N = N(G, z^1)$ as expanding exclusivity leads to an increase in cost of innovation and diminution of public domain. The net effect of a change in exclusivity on the number of inventions is eventually ambiguous. On one hand, increasing gross profits encourage inventions by rewarding investment in them. On the other hand, increased competition strains the capability of making new inventions. In terms of producer surplus accumulated by the innovating firms, this translates into an increase in producer surplus from an increase in gross profits but a decline in producer surplus from an increase in the cost of innovation. Figure 2.2 below illustrates a situation where the producer surplus and number of inventions increase while figure 2.4 illustrates a situation where they decrease.

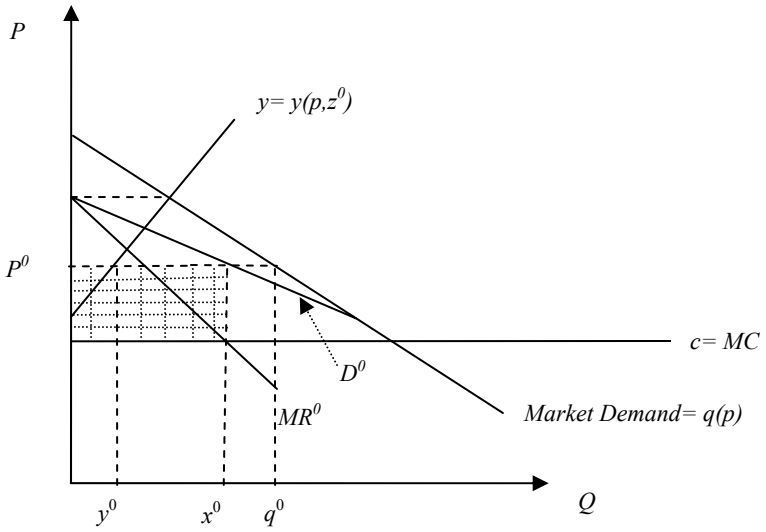


Figure 2.1: Market for drugs

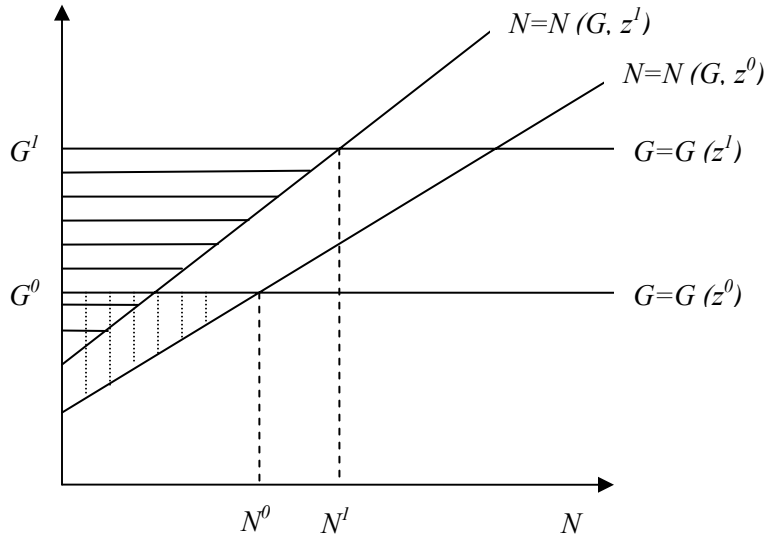


Figure 2.2: Market for new inventions

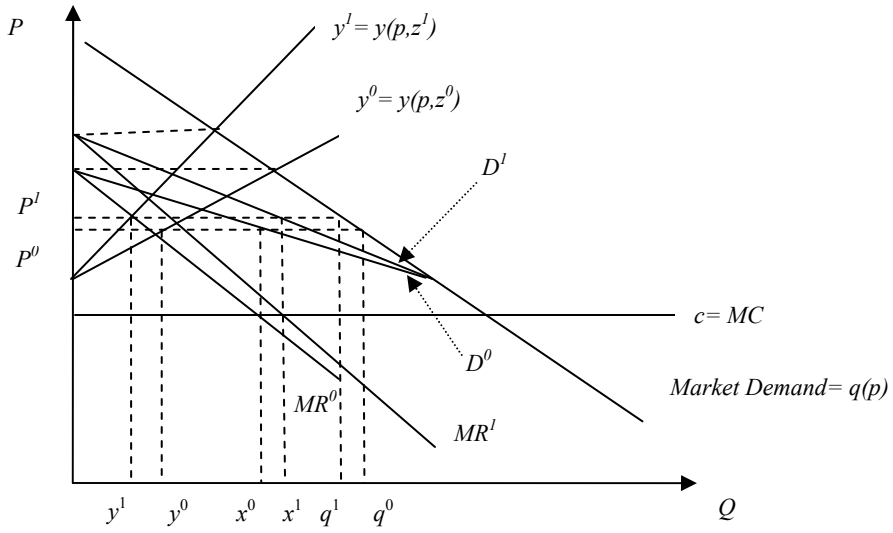


Figure 2.3- Effect of an increase in exclusivity on the market for drugs

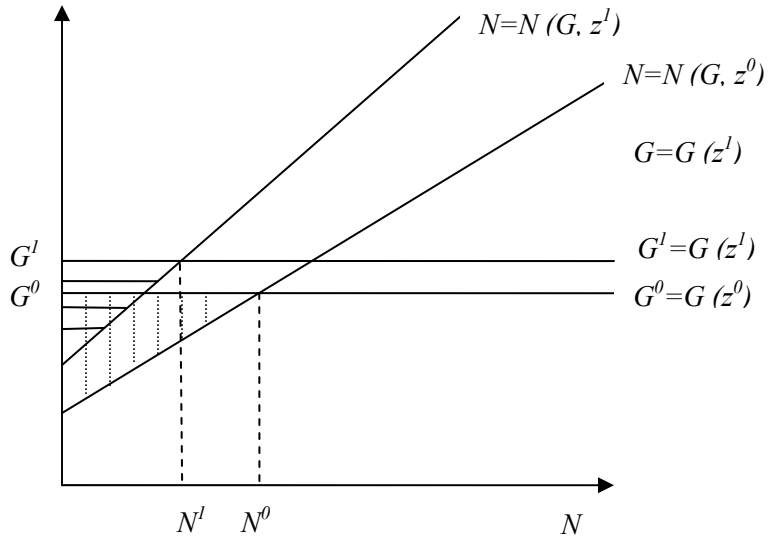


Figure 2.4 – Market for new inventions illustrating reduction in number of new inventions with an increase in exclusivity

The inventor's profit maximizing price can be obtained by differentiating equation 2.3 with respect to price p. The first order condition is given by:

$$[q(p) - y(p,z)] + (p - c)(q_p - y_p) = 0 \qquad (2.6)$$

Rearranging the above equation and using *F* to denote the fraction of units produced by the inventor *(x/q)*, *(1-F)* to denote the fraction of units produced by the producers of substitutes *(y/q)*, ε^d to denote the elasticity of market demand and ε^s to denote the elasticity of supply by the producers of substitutes, we can arrive at the following:

$$x + (p - c)\left[\varepsilon^d \frac{q}{p} - \varepsilon^s \frac{y}{p}\right] = 0$$

$$\frac{xp}{q} = (c - p)\left[\varepsilon^{\mathrm{d}} - \varepsilon^s \frac{y}{q}\right]$$

$$\left[\frac{Fp}{\varepsilon^{\mathrm{d}} - \varepsilon^s(1-F)}\right] + p = c$$

$$p\left[1 - \frac{\mathrm{F}}{\varepsilon^{\mathrm{d}} + \varepsilon^s(1-F)}\right] = c \qquad (2.7)$$

Equation 2.7 shows that the price chosen will be greater the lesser the elasticity of demand, the lesser the elasticity of supply of substitutes and the larger the inventor's share of units produced in comparison with that of the producers of substitutes. Further assuming that the second order condition is satisfied such that $S = \frac{\partial^2 \Pi}{\partial p^2} < 0$, the effect of a change in the level of protection (*z*) and a change in the inventor's marginal cost (*c*) can be obtained by totally differentiating *p* in equation 2.6 by with respect to *z* and *c* so that:

$$\frac{\partial^2 \Pi}{\partial p^2} dp + \frac{\partial^2 \Pi}{\partial p \partial z} dz = 0$$

$$\Rightarrow Sdp - y_z dz = 0,\ \frac{dp}{dz} = \frac{y_z}{S} > 0 \text{; since } y_z,\ S < 0 \tag{2.8}$$

and,

$$\frac{\partial^2 \Pi}{\partial p^2} dp + \frac{\partial^2 \Pi}{\partial p \partial c} dc = 0$$

$$\Rightarrow Sdp - \left(q_p - y_p\right) dc = 0,\ \frac{dp}{dc} = \frac{q_p - y_p}{S} > 0 \text{; since } q_p,\ S < 0 \text{ and } y_p > 0 \tag{2.9}$$

Equation 2.8 and 2.9 imply that with an increase in exclusivity and the marginal cost of production faced by the innovator, the price of a unit drug sold would rise. As the innovator's market power increases, the quantity sold would fall.

The effect of changes in exclusivity on the net returns of these firms is of particular interest in the current analysis. Conditions determining this change can be obtained by differentiating the net returns function in equation 2.3 by the index of exclusivity *z*. The change in net profits from increases in *z* can be positive or negative depending on the values taken by terms in equation 2.10

$$-(p - c) y_z - e_z \ > or < 0 \tag{2.10}$$

Here, y_z represents the reduction in the quantity produced by producers of substitutes (and is less than 0 making the first term in the above equation positive). The change in gross profits of inventors is represented by the first term in the above equation. The reduction of output, of producers of substitutes will be captured by inventors. The gross profits of inventors change by the product of this quantity captured and the difference between the price and their marginal cost. As exclusivity increases, the inventors are

better protected but at the same time the cost of innovation faced by them also increases by e_z. The sign on this net change determines the increase or decrease in the number of innovations in the market for innovations. If the sign obtained is positive it implies that the increase in exclusivity increased gross profits more than the increase in costs of innovation. This is expected to increase the number of new innovations as the net returns to innovating firms have risen. Such a result may arise if the level of exclusivity provided was low enough that increasing exclusivity enabled the inventor to retrieve profits that cover their increased innovation costs and encourage them to further innovate. If the sign taken by equation 2.10 is negative, then an increase in exclusivity would have caused the cost of innovation to rise more than any rise in gross profits and the net returns to innovating firms to fall. A fall in the net returns is expected to cause a fall in the number of innovations in the market for new innovations. Such a result may arise if the level of exclusivity provided was high enough that any further increase would translate into increased costs of innovation and significant reduction in public domain, which ends up discouraging innovative firms to further innovate.

From figure 2.2 this discussion can also be presented in net producer surplus terms. The portion which is vertically shaded represents the producer's surplus at a low level of exclusivity z^0 which yields gross profits of G^0. The producer surplus is net of the cost of innovation. $N = N(G, z^0)$ shows the supply curve for new innovation given the exclusivity level of z^0. With an increase in exclusivity to z^1 the gross profits rise to G^1 but at the same time the costs of innovation increase which are reflected by the shift backward in the supply curve. The net returns now would be the net of gross profits G^1 and the higher costs of innovation shown in the diagram by the horizontal shaded portion.

Figure 2.2 represents a case where the loss in surplus from increase in exclusivity is outdone by the gain in surplus causing the number of inventions in the market of new inventions to increase. It can be seen from figure 2.4 however, that if the gross profits do not increase as much but the costs of innovation increase a lot causing a large backward shift in the supply curve, then the loss in surplus would be greater than the gain in surplus. This situation is expected to cause the number of new inventions to fall.

Since gross profits equal the cost of innovation for the marginal inventor, equation 2.10 can be re-written in percentage terms as follows:

At the margin, $(p-c)x = e(z)$

From equation 2.10, $-(p-c)\,y_z - e_z < \text{or} > 0$

$$\Rightarrow -(p-c)\,y_z \left(\frac{z}{y}\right)\left(\frac{y}{z}\right)\left(\frac{x}{x}\right) - e_z \frac{z}{e(z)}\frac{e(z)}{z} < \text{or} > 0;$$

$$\Rightarrow -\tilde{y}_z \left(\frac{y}{x}\right)\frac{(p\text{-}c)x}{z} - \tilde{e}_z \frac{e(z)}{z} < \text{or} > 0;$$

$$\Rightarrow \left[-\tilde{y}_z \left(\frac{y}{x}\right) - \tilde{e}_z\right]\frac{e(z)}{z} < \text{or} > 0;$$

$$\Rightarrow -\tilde{y}_z(y/x) - \tilde{e}_z < \text{or} > 0, \qquad (2.11)$$

where $\tilde{y}_z$ represent the elasticity of supply by producers of substitutes with respect to a change in the exclusivity and $\tilde{e}_z$ represents the elasticity of costs of innovation with respect to a change in exclusivity. From the equation it becomes apparent that if the output produced by the producers of substitutes (y) were to fall more than the innovators output (x), then the equation is more likely to take a negative value. It can be seen from figure 2.3 that the share of producers of a substitute falls and that of innovators rises as exclusivity rises. So equation 2.11 is more likely to be negative at higher levels of

exclusivity. The gross profit enhancing effect of exclusivity reduces as the level of z rises. The inequality in equation 2.11 is also more likely to be positive the higher the elasticity of supply of substitutes with respect to changes in exclusivity. In other words, the more the marginal cost of producers of substitutes increases with an increase in exclusivity, the greater would be the gross profits that the inventor can capture. Also, from the above equation it can be seen that the higher the elasticity of cost of innovation with respect to changes in exclusivity, it is more likely that the inequality is negative. In other words, the more the cost of innovation rises with an increase in exclusivity, the lower would be the net returns and it is more likely that the number of new inventions fall.

In what follows, the framework discussed above is used in judging the impact of marginal changes in patent and regulatory protection on a set of firms involved in drug manufacturing. This is done by evaluating the abnormal returns that firms receive following events that enhance or reduce exclusivity. Cumulative Abnormal Returns (CARs) are obtained using the event study method, which is further discussed in the following section. These CARs are considered to be a proxy for the change in producer surplus of drug manufacturing firms or the net returns across firms. In case of innovative firms, this is representative of the producer surplus triangles discussed above in figure 2.2 and 2.4. CARs are then averaged across the selected set of firms to obtain Cumulated Average Abnormal Returns (CAAR), in order to evaluate how significant the event was for the industries considered. CAR is representative of the change in the present value of discounted future net returns that takes into account three components- the change in expected gross profits of future innovations, the windfall gain or loss from an increase or

decrease in the value of the existing patents of a firm from past innovations (though possibly a smaller component than the previous one) and a change in cost of innovation following a change in exclusivity. The net of these three components gives the change in net returns. With an increase in exclusivity, if the firms involved in innovation and acquisition of exclusive marketing rights exhibit a positive and significant CAAR, it may imply an expectation of increased revenue which is greater than the increase in cost of innovation. As per the above illustrations, this is expected to encourage future research and increase the number of inventions created. On the other hand, if the CAARs are significantly negative across innovative firms following an event that enhances exclusivity it may imply a smaller increase in the returns of the firms in comparison with the increase in cost of innovation.

Based on the cumulative average abnormal returns results obtained from selected changes in exclusivity, the current study tries to determine if there is any significant reaction from firms involved in drug manufacturing and innovation. Based on their reaction, inferences may be drawn regarding the effect of policies adopted in the Hatch-Waxman Act and cases that have affected patenting practices. In this study, changes in exclusivity are translated in the form of court decisions that may have affected the behavior of firms involved in making new drug innovations and firms producing generic drugs. Cases of interest and the results from event studies are discussed in the following sections.

2.3 Event Study Methodology

The event study methodology is commonly used in the finance literature in analyzing the effect on security returns of a particular event such as a stock split, dividend announcement or some external event that affects the fortune of a firm or an industry. Fama, Fisher, Jenson and Roll (1969) introduced the methodology in evaluating stock splits. Brown and Warner (1980) examine various event study methodologies in use to measure stock performance.

The market model as presented by Brown and Warner is given by:

$$AR_{it} = R_{it} - (\alpha_i + \beta_i R_{mt}) \tag{2.12}$$

where:

R_{it} = the actual return on security *i* for day *t*,

R_{mt} = the market return for day *t*,

AR_{it} = the abnormal returns for security *i* for day *t*, and

α_i , β_i = firm- specific constants.

In this model the expected firm return is a linear function of the market return using an ordinary least squares (OLS) coefficient beta. The values of α_i and β_i are computed over the estimation period using OLS. This method is adopted in the study to obtain abnormal returns of firms. Abnormal returns can then be cumulated across the days surrounding the event day according to a selected event window to obtain a cumulative abnormal return (CAR). Event windows can be selected as deemed appropriate for a given study. Further, abnormal returns that are averaged across firms in a portfolio and cumulated over a window provide us with Cumulative Average Abnormal

Returns (CAAR) which is another useful tool in analyzing the effect of an event on a portfolio or a set of firms collectively analyzed.

In this study CAR values for each event across selected drug producing firms in an industry act as a proxy for the net returns that have been analyzed in the theoretical model presented in section 2.2. The Abnormal Returns in a sense represent the present value of expected returns on securities. The CARs aggregated across firms and over a relevant window can help evaluate the net effect of an event over the selected set of firms in an industry and evaluate the significance of this effect.

2.4 Data

This study considers sets of firms belonging to three industries- pharmaceuticals, biotechnology and generic drug manufacturers. Pharmaceutical firms and biotechnology firms are considered to comprise the innovative firms which are involved in the process of creating patented drugs and acquiring exclusive rights in marketing innovative drugs. Pharmaceutical firms are typically involved in the process of developing and researching new drugs and medications used to cure illnesses. Biotechnology firms are also involved in extensive research of biological substances which can be used, among other uses, in finding cures for illnesses. Both pharmaceutical firms and biotechnology depend on patenting their inventions so as to appropriate returns on their research efforts. A set of generic drug manufacturing firms is also included here to represent the producers of substitute drugs as discussed in the model above. The set of firms considered are presented in tables A, B and C in Appendix A. Table A presents the top 20 biotechnology firms in terms of market share, which represent about 70 % of the industry market

share[24]. The market here comprises of all the firms listed under the SIC code of 2836 for firms involved in the production of biological products. Table B lists the top 15 pharmaceutical firms representing 90% of the industry market share. The market share in this case comprises all the firms listed under SIC code 2834 for pharmaceutical preparations. Besides these firms, a set of 17 generic firms are also included in the analysis as listed in table C[25].

The events considered in the study are a set of court decisions that have been compiled from the CRS issue briefs for congress (compiled by Schacht and Thomas following the passage of the Hatch-Waxman act)[26], 'Guidance for Industry' publications issued by the FDA and discussions on these reports[27], law publications[28] and advice from a legal expert in this area[29]. These sources particularly identify the listed cases as being particularly influential in the regulatory environment formed by patent law, Hatch-Waxman and Orange Book listings. The list of events is presented below in table 2.3. Decision dates of the cases have been used as the event dates in the event studies.

[24] Market share here is computed as the percentage of total sales of firms in the selected set, over the total industry sales. The same firms also dominate the market in terms of R&D contributing nearly same percentages to the industry R&D expenditure.
[25] Some of these firms however drop out of the analysis for events prior to or on 1990 due to data restrictions. The numbers dropped are presented in the event study results. The firms selected here are among top generic firms listed and traded on as per Yahoo finance in 2005.
[26] CRS Reports for Congress (Dec 2000 update), (April 2002 update)
[27] FDA and CDER guidance reports (March 2000), Link: http://www.fda.gov/cder/guidance/3659fnl.htm ; Parise and Pezzano (March 2000), Link: http://www.morganfinnegan.com/news/articles_publications/0070
[28] Caffrey and Rotter (2004); Range (2001), Link: http://www.law.harvard.edu/faculty/hutt/book_index.html ; Lietzan (2004), pg. 287; Derzko (2005) pg. 165; Greene (2005) pg. 309; Wharton (2003) pg. 1027.
[29] Guidance and assistance from Charles T. Joyner, Attorney at Law is gratefully appreciated.

2.5 Results

Event Studies for the selected sets of firms considered in this study are run using the EVENTUS package provided by Wharton Research Data Services (WRDS). The EVENTUS package performs event studies using data read directly from the CRSP stock databases. Daily stock values are considered in the analysis. Estimates use the default estimation process in EVENTUS which is the market model estimated by Ordinary Least Squares (OLS) using data from a 255 trading-day estimation period ending 46 trading days prior to the event date. For this study the returns are analyzed over two short event windows of day 0 to day 1 (0,1) and day -1 to day 1 (-1,1), based on the idea that the decision of the court is quite uncertain in nature and the courts try to keep the information secret until the day of the decision. Markets are also considered efficient in reacting to this information instantaneously. The returns over event window (-1, 1) are also analyzed here to allow for the possibility of leakage around the event day. Using EVENTUS, only the Cumulative Average Abnormal Return (CAAR) values for the set of firms considered are presented below so as to analyze the overall effect of the case in the industries considered. EVENTUS also provides values for two test statistics that are used in this study for analysis. A parametric test statistic (Patell Z test) and a non-parametric test statistic (generalized sign test) are presented[30]. The Patell Z test formulated by J.M.Patell is an example of a standardized abnormal return approach, which makes a mean zero and constant standard deviation assumption under the null hypothesis for the abnormal return value of each security. A separate standard error is computed for each of the security-events, which are also assumed to be cross-sectionally independent. The generalized sign

[30] Refer Patell (1976), Cowen (1992) for details about these two tests.

test formulated by A.R. Cowen compares the proportion of positive abnormal returns around an event day to the proportion from the estimation period and tests if they are significantly different[31]. Results of these tests are qualitatively similar to student t tests.

The results of the event studies are presented in the following pages. Table 2.1 gives a list of the cases included. 16 cases of interest are considered here. Although event studies were run using all the cases listed below, the events that turned out having significant effects are discussed first in detail along with their results. Each event is presented separately with a short summary about the case, some discussion on the expected effect of the case along with some associated literature on it, and analysis of the actual results obtained on aggregate. As listed in the table, patent related cases are discussed first and then the Hatch-Waxman cases are considered. Within the Hatch-Waxman cases, issues on 180-day exclusivity provisions, Orange Book listing disputes and the practice of evergreening are addressed.

[31] The null hypothesis for the generalized sign test is that the fraction of positive returns is the same as in the estimation period. For example, if 46% of market adjusted returns are positive in the estimation period, while 60% of firms have positive market adjusted returns on event day -1, EVENTUS reports whether the difference between 60% and 46% is significant at the 5%, 1%, or $1/10^{th}$ of 1% level. The actual test uses the normal approximation to the binomial distribution.

Table 2.1: List of events

Cases considered		Event date- Case decision day
	Patent related cases:	
1	Diamond v Chakrabarty [447 U.S. 303] +	June 16th 1980
2	In re Pleuddemann [910 F.2d 823] +	Aug 3rd 1990
3	In re Brana [51 F.3d 1560] *	March 30th 1995
4	Warner Jenkinson v. Hilton Davis [520 U.S. 17]	March 3rd 1997
5(a)	Festo v SMC -1 (Federal Circuit) [234 F.3d 558] *	Nov 29th 2000
5(b)	Festo v SMC -2 (Supreme Court)[535 U.S. 722]	May 28th 2002
	Hatch-Waxman related cases:	
	(180-day market exclusivity related)	
6(a)	Mova v Shalala(District) [955 F. Supp. 128 (D.D.C. 1997)] *	Jan 23rd 1997
6(b)	Mova v Shalala(Federal Circuit) [140 F.3d 1060] *	April 14th 1998
7	Purepac Pharm co. v Friedman [162 F.3d 1201(D.C. Cir. 1998)]	Dec 29th 1998
8	Apotex v. Shalala [53 F. Supp 2d 454 (D.D.C 1999)]	June 16th 1999
9	Mylan v. Shalala [81 F. Supp. 2d 30] *	Jan 4th 2000
	(Orange book listing disputes)	
10	Mylan v. Thompson[268 F.3d 1323]	Oct 12th 2001
11	Andrx v Biovail[276 F.3d 1368] *	Jan 17th 2002
12	In re Buspirone [185 F.Supp. 2d 363 (S.D.N.Y)] *	Feb 14th 2002
13	Apotex v. Thompson [347 F. 3d 1335 (Fed Cir. 2003)] *	Oct 27th 2003
	(Evergreening related issues)	
14	Ben venue v Novartis[10 F. Supp. 2d 446] *	June 23rd 1998
15	Warner Lambert Co. v. Apotex Corp [316 F.3d 1348 (Fed Cir. 2003)] *	Jan 16th 2003
16	Schering Corp. v. Geneva Pharms. Inc. [339 F.3d 1372 (Fed Cir. 2003)] *	Aug 1st 2003

+ These events occur prior to or in 1990 and face a larger number of firm-drops due to lack of data availability or firms not existing at that time.
* Cases returning significant results.

Patent related cases that returned significant results:

1. In re Brana [51 F.3d 1560] March 30th 1995:-

Table 2.2.1: In re Brana

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.06%	5:9	-0.985	-0.857
(-1,1)	-0.61%	5:9	-0.982	-0.857
Firms dropped out of 20	6			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-2.05%	1:10<	-4.002***	-2.575*
(-1,1)	-3.43%	0:11<<	-5.372***	-3.179**
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	2.41%	4:5	0.969	-0.203
(-1,1)	0.43%	4:5	-0.072	-0.203
Firms dropped out of 16	7			

The symbols $,*, ** and *** denote statistical significance at the 0.10, 0.05, 0.01 and .001 levels respectively, using a 2-tail test. The symbols (, < or), > etc. correspond to $,* and show the significance and direction of the generalized sign test.

Miguel F. Brana along with other applicants, appealed the decision of the United States Patent and Trademark Office (USPTO) Board of Patent Appeals (or the Board) rejecting claims on certain chemicals in their patent application. Their application stated that the compounds had useful properties as anti-tumor substances. The Board rejected the patents claims on two grounds. First, the applicant's specification failed to disclose a specific disease against which the claimed compounds are useful, which precludes anyone skilled in the art from using the invention. One of the contentions of the Board was that the test was conducted using lab mice by inducing the tumors into them rather than testing a real disease. Secondly, the Board argued that the applicant had not conducted sufficient tests to prove the compound useful as the tests were pre-clinical in

nature and not predictive of success in treating cancer in humans. The usefulness of the compound was called into question. The Federal Circuit was however of the view that the inventor need not wait till a human develops a disease naturally before finding a cure for it. The phase two clinical tests of safety and efficacy were not prerequisites as per patent lay to find a compound useful. The tests were an FDA requirement. It warns that if phase two tests were to be a requirement to prove utility in human therapy for patentability, the associated costs would be high enough to "prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many critical areas such as the treatment of cancer." This case highlights allowance of patenting at an earlier stage in the drug development process. In re Brana recognizes that pharmaceutical inventions, at the time that patent applications are filed, necessarily require further research and development even before administration to humans for testing.

Expected effect: In accordance with the opinion of the court it appears as though the court believes early patenting to be an incentive for research. This is because requiring phase two safety and efficacy tests as a benchmark for having proven utility in patenting terms, is viewed by them as costly enough to discourage research. Alternative opinions however support the "anti-commons" argument. As Merges and Duffy (2002)[32] point out, early patenting may lead to an undesirable consequence of encouraging patent races that could be socially undesirable. In areas like biotechnology, the number of researchers capable of discovering cDNA sequences may be large. Finding a use for the sequences may be a harder step to take. Researchers capable of finding a use for a cDNA sequence

[32] Merges and Duffy (2002) pg. 254-258.

when its uses are largely unknown, would probably be more deserving of appropriating rents from that use. Otherwise, the patenting process would encourage biotechnology firms to enter onto races to isolate DNA sequences and patent them. Numerous separate cDNA patents may be wasteful if these discoveries were complementary. Patents on different proteins could end up blocking one another and become a hindrance to furthering the research process as numerous licensing agreements would have to be entered into. This problem is also often referred to as the "anti-commons" problem where property gets underused as the number of property rights increase. As per Merges and Duffy, the anti-commons problem makes a case for patenting requirements being tighter in finding utility in an invention. They argue that the utility requirement has to do with the timing of when an invention becomes useful. In such a circumstance a patent would not be conferred until a substantial use has been identified hence leading to later patenting.

Another aspect of this above argument has to do with the scope that the patent would confer. Allowing a firm to patent a compound that has been recognized to have anti-tumor properties without exactly having determined a particular disease or cancer that it can claim to cure, a large disease area would fall under the domain of such a patent. It would be possible to test for every subsidiary disease area and patent the compound for each test that returned a positive result. A competing research firm would have to obtain a license to conduct a similar test for a particular cancer using the compound. This decision may therefore have the effect of conferring a broad patent scope to firms and blocking other firms in their research activities.

From the results it appears that the Biotechnology firms together show an insignificant and nearly zero reaction over the two windows. Pharmaceutical firms on the other hand show significant negative reaction. Generics show a positive insignificant effect over (0, 1) window which is dominated by Hi tech Pharmacal but with no particular coinciding news event. A look at the individual firm reaction in the biotechnology portfolio shows that Imclone and Medarex exhibit exceedingly positive responses over the two windows with little significance [Imclone - window (0, 1): CAR= 24% (significant at 10%), window (-1, 1): CAR= 14%; Medarex - window (0, 1): CAR= 15% (significant at 5%), window (-1, 1): CAR= 15% (significant at 10%)]. Protein Design labs also reacted positively over the (-1, 1) window (CAR= 7%) but reacts negatively over the (0, 1) window (CAR= -9%) which is significant at 10%. Xoma reacts very negatively over the two windows significant at 1% [window (-1, 1): CAR= -20% (significant at 1%); window (0, 1): CAR= -24% (significant at 1%)]. I couldn't find any news events corresponding to these stocks possibly explaining these movements except for Protein Design Labs that reported strong phase 3 data on one of its drug[33]. Removing PDL raises net negatives for the (-1, 1) window (CAAR= -1.23%) while the (0, 1) window is slightly positive (CAAR= 0.79%) neither of which is significant. In summary, the biotechnology firms seem quite volatile over this time period but nothing very conclusive can be said.

The significant negative reaction of pharmaceuticals however is in support of the anti-commons argument laid out previously and qualifying a need for a stronger utility requirement for patenting. Innovators in the pharmaceutical sector may view early patenting rights to firms in the industry as blocking their research initiatives with higher

[33] 'PDL up on hopes for strong Phase III data", Jesse Eisinger, Dow Jones news, 29th March 1995,

licensing costs to be incurred. Early patenting may represent loss of patentable domain to pharmaceutical patenting firms. It is also possible that this reaction is representative of the long and unpredictable nature of drug development and obtaining marketing approval from FDA. The onus would now lie on the pharmaceutical firms to decide upon the right time to patent their inventions so as to efficiently use the life of the patent. The drug development stage usually tends to be long. If pharmaceutical firms choose to patent early, they may lose some of this time and money on the regulatory process of obtaining drug approval. Allowing early patenting at the early stages of drug development may act as a signal to go ahead into the following stages but might also leave a shorter exclusive marketing period which is possibly of more consequence in drug marketing.

2. Festo- Federal Circuit [234 F.3d 558] Nov 29th 2000:–

Table 2.2.2: Festo (Federal Circuit)

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	3.66%	15:3>>	1.691$	3.124**
(-1,1)	5.15%	14:4>>	2.031*	2.652**
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.86%	7:5	0.969	0.693
(-1,1)	1.80%	9:3)	1.527	1.848$
Firms dropped out of 14	2			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	1.97%	7:2>	0.762	1.979*
(-1,1)	2.87%	6:3	1.081	1.309
Firms dropped out of 16	7			

This case focused on clarifying the Federal Circuit's stance on the relation between two patent law concepts, the doctrine of equivalents and the rule of prosecution

history estoppel. Prior to Festo this relation had been considered in a separate case by the Supreme Court (in Warner Jenkinson Co. v. Hilton Davis Chemical Co., 520 U.S. 17 (1997)). In that case, the doctrine of equivalents was called to question because of the uncertainty in the allowable range of equivalents to an invention. This had made the determination of a permitted and an infringing alternative difficult. Also in that case, the Supreme Court had held that, 1) the doctrine of equivalents must be applied to individual elements of the claims and not to the invention as a whole, 2) "Prosecution History Estoppel"[34]- a rule which provides that under some circumstances, a surrender of subject matter during a patent prosecution precludes recapturing any part of that subject matter, even if equivalent to the matter expressly claimed- continued to be available in defense to patent infringement; and 3) if a patent holder demonstrates that an amendment required during prosecution had a reason unrelated to patentability, then a court must consider the reason in order to decide whether the prosecution history estoppel is precluded.

In the Festo corp. v SMC, Federal Circuit and Supreme Court cases, the issue of this relation between prosecution history estoppel and the doctrine of equivalents resurfaced. The Federal Circuit in its decision tried to further increase the certainty regarding the application of Prosecution History Estoppel and reined in the Doctrine of Equivalents. Festo corp. owned two patents for a magnetic rodless cylinder each of which was amended during patent prosecution and two new limitations were added: the inventions contained a pair of sealing rings and the second patent had an added limitation regarding the composition of a "sleeve" of the device. SMC, a competitor entered the market with a similar device except that their device employed a single sealing ring and

[34] The prosecution history is a public record of the patent proceedings giving details on any amendments made to the patent application before getting approval.

the “sleeve” was of a different composition. Festo brought a suit against SMC in the US District Court for the district of Massachusetts arguing that the competitor’s device was similar enough to be infringing their device. The District Court found the device infringing which was affirmed by the Federal Circuit on appeal by SMC. The Supreme Court however remanded the case in 1997 in light of their ruling in Warner-Jenkinson and held that the competitors could rely on the prosecution history of the patent to stop the patentee from recapturing subject matter that may have been surrendered by an amendment to the patent application in order to obtain the patent. On remand, the Federal Circuit in the decision being currently considered in this event study, reversed the district court judgment and prevented Festo from asserting infringement under the doctrine of equivalents and made two further clarifications. The two matters requiring clarification were: First, do all amendments during prosecution, even clerical ones, create prosecution history estoppel, and second, when an amendment is made to a prosecution what is lost − all arguments that anything is equivalent to it or only what is related to the reasons for claim amendment? Federal Circuit held that any amendment made regardless of the reason that caused the scope of the claim to be narrowed could give rise to prosecution history estoppel. Secondly, a claim once narrowed presented an “absolute bar” to coverage for all equivalents to the amended limitation. Besides claiming subject matter, a patent application is also required to describe the best mode of carrying out an invention. Changes made to the form of the application rather than the subject matter that narrow a claim, even if made with the intention of providing a better description, would be subject to estoppel as this would imply an inability on the part of the patent applicant to claim a broader subject matter. As per the absolute bar requirement, an estoppel bars all claims of

equivalence to the narrowed element and would promote certainty in the determination of infringement cases. The Federal Circuit acknowledges that this was a stricter requirement in comparison with the relatively flexible bar adopted by the courts in the past. The flexible bar closed some but not all claims of equivalence depending on the purpose of the amendment and the alterations in the text. However, the Federal Circuit believed that the absolute bar that they now established, would lend certainty to the claims.

Expected Effect: Following this decision, patentees may have found themselves having relinquished some of the equivalents to a limitation that was amended in the past. The case seems to expand the prosecution history estoppel and patentees may have to be careful in the way they write their patent claims to avoid having any amendments going into their prosecution history.[35] Dissenting judges in this decision also point at how the case would unsettle the expectations of existing patentees. This case may be particularly severe for industries like pharmaceuticals and biotechnology that rely heavily on patents. The patent application process tends to be more elaborate in their case and revision of claims is not unusual. Such firms tend to follow the practice of writing broad claims in their applications. Any amendments to those claims become a part of their prosecution history. Following the Federal Circuit decision they may have inadvertently relinquished some of their claims due to the prosecution history.

The event study results show that Biotechnology firms, Pharmaceuticals and Generics react positively over the event windows. These values are significant in case of biotechnology firms though not so much in case of pharmaceuticals. The results may uphold the possibility of a narrow patent protection causing a decrease in cost of

[35] Lowrie and Topper (2002). Link: http://www.wolfgreenfield.com/media/news/news.12.pdf

innovation that overwhelms the revenue loss from narrowing of patents. As claims are constructed in a tighter manner, firms may actually find new areas of patentability. The positive reaction of generics may be reflective of the benefits they accrue from lower likelihood of being charged with infringement. Among biotechnology firms Abgenix showed an exceptional positive reaction on day 1. One of its drugs received an orphan drug status which may explain this to some extent[36]. Removing Abgenix from the portfolio only slightly changes the results over the windows [window (0, 1): CAAR= 3.47%, window (-1, 1): CAAR= 5.21%] and continues to return significant Patell and Generalized Sign test results.

The Festo Supreme Court decision was also the subject of an event study, but returned insignificant results. This result is further discussed in a later section of this chapter along with other cases that returned insignificant results.

FDA and Regulatory environment related issues that returned significant results:

Hatch-Waxman: 180-day market exclusivity and some related cases

As discussed in the introductory chapter, under the 1984 Hatch-Waxman Act statutes, the 180-day exclusive marketing period is rewarded to the first generic firm that seeks approval of its Abbreviated New Drug Application (ANDA) by filing a paragraph-four certification. A paragraph-four certification allows a generic drug manufacturing firm to seek immediate approval of its ANDA from the FDA. In a paragraph four filing, the applicant asserts that the patent under issue is invalid or will not be infringed by the manufacture, use or sale of the generic drug for which the ANDA is being submitted. The patent holder is allowed to bring an infringement suit against the ANDA applicant within

[36] Abgenix, SangStat transplant drug awarded orphan drug status, 30th Nov 2000, Dow Jones news

45 days of its receiving notification from the ANDA applicant of such a certification. If the ANDA applicant is sued, the FDA suspends approval of the ANDA until:

1. the date of the court's decision that the listed drug's patent is either invalid or not infringed; or
2. the date the listed drug's patent expires, if the court finds the listed drug's patent infringed; or
3. subject to modification by the court, the date that is thirty months from the date that the owner of the listed drug's patent received notice of the filing of a paragraph –four certification.

If the generic drug manufacturing firm prevails, the Act provides a 180-day exclusive marketing period to the first generic applicant to file a paragraph-four certification. This is done with the intent of rewarding the generic manufacturer for identifying and litigating a wrong listing and encouraging them to do so. The exclusivity period is triggered if one of two statutory conditions is met,

1. A court decision finding the patent to be invalid, unenforceable, or not infringed by the ANDA product; or
2. The first commercial marketing of the ANDA product.

Various issues arose following the passage of the Hatch-Waxman Act particularly related to the FDA's interpretation of the statute in its process of approval. Following are the event study results on some of the cases which discuss issues related to the 180-day exclusivity provision and how the courts resolved them. Of particular interest is the effect of these decisions on the exclusivity enjoyed by patenting firms.

3(a). Mova vs. Shalala [955 F. Supp. 128 (D.D.C. 1997)] Jan 23rd 1997:-

Table 2.2.3(a): Mova v. Shalala (District level)

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.25%	4:12(	-0.975	-1.653$
(-1,1)	-0.23%	6:10	0.118	-0.649
Firms dropped out of 20	4			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.76%	2:9<	-2.902**	-1.979*
(-1,1)	-0.12%	3:8	-0.123	-1.375
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.95%	5:4	0.246	0.501
(-1,1)	0.08%	5:4	-0.286	0.501
Firms dropped out of 16	7			

In this case, Mova Pharmaceutical Corp. sues to compel the FDA to withdraw or change the effective date of its early approval of an Abbreviated New Drug Application (ANDA) submitted by Mylan Pharmaceuticals Inc. The dispute arose because of the 180-day exclusivity provision in the Hatch-Waxman Act and its implementation by the FDA. Mova Corp., a generic drug manufacturing company, had filed an application for marketing a generic version of a drug but was not approved since Pharmacia and Upjohn Co. file a suit against Mova alleging that it infringed a patent on the drug that belonged to them. Meanwhile, Mylan pharmaceuticals also applied to the FDA to market another generic version of the same drug under a paragraph four certification and received immediate approval. Mylan also wasn't sued by Upjohn for its paragraph four application. Following this, Mova brought a suit in the District Court for the District of Columbia to compel the FDA to delay the effective date of this approval until 180-days after the day that Mova won its suit or began to market its product, whichever was earlier,

as per the provisions of the Hatch-Waxman statutes. The FDA essentially interpreted the paragraph-four provision to mean that in case of a patent infringement suit filed by a patent holder against the first ANDA applicant, "successful defense" by the ANDA applicant was required for them to avail themselves of the 180-day exclusivity period regardless of whether they were the first to file this claim. This permitted the FDA to approve Mylan's application. Mova challenged that the FDA's interpretation of the paragraph-four provision requiring "successful defense" was incorrect and inconsistent with the language of the statute. The District Court ruled in favor of Mova and granted preliminary injunction to the approval of Mylan's ANDA prior to the approval of Mova's ANDA which was filed first. It held that the 180-day exclusivity statute was not worded in a manner so as to require "successful defense" by the first generic applicant that ends up getting sued for patent infringement. The 180-day exclusivity statute is provided with the intention of rewarding the first generic to enter the market, under a paragraph- four certification. Following the FDA's interpretation, that would not be the result.

Expected effect: This case addresses the inconsistency in the FDA's interpretation of the 180-day exclusivity statute of Hatch-Waxman Act. The court disagrees with the FDA's interpretation that the first company to apply for an ANDA under the paragraph four certification if sued, had to "successfully defend" itself in order to receive the 180-day exclusive marketing period. Following this decision the first generic firm to file a paragraph-four certification would be eligible to obtain the exclusivity period regardless of its being sued later. The decision appears to encourage early and easier entry to generics as generic drug manufacturing firms rush to obtain the first-to-file status under

paragraph-four certification. This may also have a negative effect on revenues of innovative firms like biotechnology and pharmaceuticals.

From the results it can be noticed that the cumulative effect for the two windows is negative for biotechnology firms and pharmaceuticals while generic drug manufacturers don't react much. Also neither window returns significant results for generic drug manufacturers. Pharmaceuticals seem to react significantly but the results for biotechnology firms are not very significant. The negative change in returns for pharmaceuticals seem to point at the losses they face from easer competition and a bigger revenue loss effect that may potentially discourage new innovations.

3(b). Mova v. Shalala – Federal Circuit [140 F.3d 1060] April 14th 1998:-

Table 2.2.3(b): Mova v. Shalala (Federal Circuit)

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.14%	8:9	0.063	0.032
(-1,1)	-0.74%	6:11	-0.634	-0.941
Firms dropped out of 20	3			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-2.75%	0:1<<	-3.636***	-3.136**
(-1,1)	-2.84%	0:1<<	-3.110***	-3.136**
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.27%	4:5	-0.080	-0.018
(-1,1)	0.18%	4:5	0.005	-0.018
Firms dropped out of 16	7			

Mylan and the FDA appealed the District Court decision in the previous case at the U.S. Court of Appeals for the District of Columbia. Mylan appealed the first-to-file decision of the District Court. The U.S. Court of Appeals for the District of Columbia

affirmed the District Court's decision that the FDA's regulation of "successful defense" acted beyond its authority as per the statute.

While's Mova's request for preliminary injunction was pending, Upjohn had filed a motion to intervene in the litigation. The District court had however denied Upjohn's motion based on its view that Upjohn did not have a legally protected interest in the subject matter of the litigation. Upjohn appealed this decision and the U.S. Court of Appeals for the District of Columbia consolidated this appeal with that of Mylan and FDA. The U.S Court of Appeals concluded that the District Court erred in its decision to deny Upjohn's motion. Upjohn is entitled to participate in this and any further proceedings before the district court since it is had particular interest. It faced the possibility of losing its market to Mylan if the district court had denied the injunction and allowed Mylan's product on the market prior to a decision about Mova's application.

Expected effect: The expected effect here is similar to the previous case since the U.S. Court of Appeals for the District of Columbia affirms the district court's decision against the "successful defense" interpretation by the FDA of the 180-day exclusivity statute. The court's acknowledgement of Upjohn's interest in the case however also highlights some issues raised by critics of the decision. Critics argue that the first-to file decision of the courts would lead to sham ANDA applications through which generics would race to file first to avail themselves of the 180-day exclusivity provision regardless of the validity of the application[37]. In situations where the generic that is first-to-file is sued, the entry of the rest of the generics gets stalled till the date a court decision is arrived at or the first filer chooses to commercially market its product. In cases where the first-to-file

[37] CRS issue Brief for Congress (Jan 5th 2004 update) pg. 4; Eisenberg (2001); Engelberg (1999) pg. 389.

is not sued by the patent holding firm nor does it begin marketing its product, other generics can essentially be blocked from entering till the patent expires. Such a possibility can lead to collusive behavior among few generics and patenting firms so as to extend the market exclusivity to patent holding firms in exchange for some settlements. Even if the patent holding firms manage to form a blocking coalition, they would however end up losing large amounts of their funds on patent settlement payments or procuring duopoly returns over the remaining patent term.

The results show pharmaceuticals incurring significant negative CAARs. This result seems to uphold the possibility of patenting firms losing as a consequence of the decision, be it through loss of revenues or higher transaction costs in order to maintain duopoly returns. The individual pharmaceutical securities reacted consistently negatively with seemingly no anomalies. Pharmaceutical firms in effect react negatively to this regulatory change that eases generic entry and reduces exclusivity. Biotechnology firms don't react very much over the two windows. Protein Design Lab showed some exceptionally positive Cumulative Abnormal Returns over the (0, 1) window (9%). A possible news item to support these results is news of insider trading [38] Removing PDL only slightly increased the negatives over the windows [window (0, 1): CAAR= -0.52%, window (-1, 1): CAAR= -0.78%] but they remain insignificant.

[38] 'Insider sells Protein design Labs inc. stock', Dow Jones News, 14th April 1998.

4. Mylan Pharm inc. v Shalala [81 F. Supp. 2d 30] Jan 4th 2000:-

Table 2.2.4: Mylan v. Shalala

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-4.82%	2:14<<	-3.397***	-2.630**
(-1,1)	-5.41%	2:14<<	-2.811**	-2.630**
Firms dropped out of 20	4			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.24%	5:6	-0.386	-0.208
(-1,1)	-1.36%	4:7	-1.410	-0.811
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.23%	5:4	-0.330	0.535
(-1,1)	0.80%	3:6	-0.410	-0.802
Firms dropped out of 16	7			

This is another case clearing up regulatory ambiguity. It clears an ambiguity regarding the "court decisions" trigger to the 180-day exclusivity period to start. Here Mylan was a second ANDA applicant attempting to enter Abbott's market on a branded drug. The first ANDA applicant, Geneva Pharmaceuticals Inc., filed a paragraph- four certification and got subsequently sued by Abbott. The Northern District of Illinois District Court granted Geneva's motion for summary judgment and declared Abbott's patent invalid. Abbott appealed this decision but the Federal Circuit affirmed it on a later date. Geneva however started marketing its drug prior to the Federal circuit hearing. Meanwhile, Mylan filed the second paragraph-four certification. Abbott sued Mylan but the Northern District of Illinois District Court also ruled in favor of Mylan. Abbott appealed this decision as well but the District Court's decision was affirmed. Following this, the FDA tentatively approved Mylan's drug to be marketed 180 days after the day Geneva started commercial marketing. Mylan contested this decision at the D.C. District

court since it believed that it should be entitled to approval following 180-days after the District Court's decision in favor of Geneva which occurred prior to Geneva's decision to market. The D.C. district court rejected the FDA's position that the triggering event is "either the date that a district court decision is affirmed by the federal circuit or the date on which the time for filing an appeal has lapsed." The court in other words held that "decision of court" includes "the decision of a United States district court regardless of whether the decision is appealed". So, the exclusivity period starts to run on the date of a district court decision finding invalidity or non-infringement.

Expected Effect: This case like the previous case clears another ambiguity and eases the process of entry of generic drug manufacturing firms. In case a patent is found invalid or non-infringed, it acts as a triggering event and subsequent applicants can enter faster. Though a generic drug manufacturing company could choose to delay market entry in order to avoid risking damages it might incur if the district court's ruling of invalidity or non-infringement is overturned, it may face a bigger risk of losing the exclusivity period if it waits too long in taking action as the statute puts bars on the time available to the generic drug applicant in exercising the exclusivity provision. In most cases they may end up choosing to start marketing[39]. So while some generic firms (second and later filers) are expected to be benefited by early entry others (first filers) may lose since they may face either a shortened exclusivity period or a substantial risk. NDA holding patenting firms may be affected negatively with easier and early competition. Also, if the decision of a lower court is later overturned they would have faced losses in market share and revenue.

[39] Greene (2005), pg 309.

The results above seem to follow expectation in case of biotechnology firms which turn out quite significant. Pharmaceuticals react negatively but it turns out insignificant. Generics don't react much.

In summary, three out of the five 180-day exclusivity cases seem to have shown some significant reaction from biotechnology or the pharmaceutical firms with abnormal returns falling following regulatory events that appear to reduce exclusivity by easing the process for generics to avail themselves of the 180-day exclusivity period, or clearing ambiguities in their availing themselves of this exclusivity period. Patenting firms may have faced large losses in revenues which outdo any gains from lowered costs associated with knowledge gain or lowered licensing and listing costs. On the other hand, as discussed in case of Mova, if the patenting firms enter into blocking coalitions with generic drug manufacturers, they can possibly protect their market from immediate generic entrance for some time but would have to do this in exchange for large patent settlements and transaction costs. The results seem to indicate that patenting firms incur a negative effect on their net surplus and may be discouraged in their inventive process. Further analysis using regressions on R&D may also be informative in making judgments about changes in research following changes in these regulatory events that effect expectation of future returns.

Orange Book listing litigation procedure and related disputes that returned significant results:

Provisions of the Hatch-Waxman Act also brought attention to the improper Orange Book listings that were made by patent holding firms and the fact that the FDA was ill-equipped in checking on the propriety of their claims. The FDA oversees listings on the Orange Book. The Orange Book lists products that have been fully reviewed by the FDA for safety and efficacy and for which New Drug Applications (NDA) have been approved. Following Hatch-Waxman Act, the book also lists approved generic drug products along with information about patents on NDAs and periods of marketing exclusivity. FDA had maintained that it plays only a ministerial role in the listing process of the drugs and does not have the expertise to address patent issues or analyze whether the patents listed by NDA applicants actually claim the drugs or applicable methods of using those drugs. Generics on the other hand were provided with insufficient means to question a particular Orange Book listing or seek to delist a wrongful listing. Following cases discuss some issues that arose consequentially along with their event study results.

5. Andrx v. Biovail [276 F.3d 1368] Jan 17th 2002:-

Table 2.2.5: Andrx v. Biovail

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-3.98%	2:16<<<	-2.894**	-3.308***
(-1,1)	-3.65%	4:14<	-2.177*	-2.365*
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.11%	6:7	-0.091	-0.307
(-1,1)	-0.47%	5:8	-0.482	-0.861
Firms dropped out of 14	1			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.30%	3:8	-0.337	-1.357
(-1,1)	0.00%	5:6	-0.096	-0.149
Firms dropped out of 16	5			

This case illustrates a problem with the FDA's Orange Book listing process that allowed a brand name manufacturer to claim extended protection on its listing. Andrx Pharmaceuticals attempted to market a generic version of Biovail Corporation's brand drug, Tiazac. Andrx filed a paragraph-four certification in 1998. Biovail sued for infringement, triggering a thirty-month stay, but lost the infringement action in a ruling affirmed by the Federal Circuit in 2001. While the infringement suit was still pending, Biovail obtained rights to a patent for an extended release form of the active ingredient of Tiazac, and listed this patent in the Orange Book which enabled it to extend its protection on this drug. As a result, the FDA indicated that it would not be approving Andrx's ANDA upon the expiration of the 30-month stay.

Andrx sought a declaratory judgment that it had not infringed the newly filed patent as it was invalid, and sought delisting of the patent from the Orange Book and shortening of the 30-month period. It also filed another paragraph- four certification on

February 16th, 2001 that it did not infringe the new patent and that it was invalid. The US District Court for the District of Columbia ruled that an action to delist a patent from the Orange Book was not allowable since it served as a private enforcement of the Federal Food Drug and Cosmetic Act (FFDCA) which was not available under the Hatch-Waxman Act. However it held that Biovail's action with regard to the new patent was done with the intention of delaying approval of the ANDA and ordered the FDA to shorten the 30-month stay but stayed the order so Biovail could seek review.

Biovail appealed this holding at the US Court of Appeals for the Federal Circuit. The Federal Circuit agreed that the current regime led to a major problem since Biovail succeeded in unlawfully delaying Andrx's entry by listing a patent that could not have covered Tiazac, since the technology that the patent claims was developed after the marketing of Tiazac. The Federal Circuit however was of the view that the District Court had no authority to shorten the statutory 30-month stay in an infringement action and vacated this order. It remanded the case for further proceedings while suggesting another judicial avenue for generic manufacturers seeking to delist patents listed on the Orange book under the Administrative Procedure Act, or APA. The APA is a general statute that in part allows adversely affected individuals to seek judicial review of an agency action. Following this it would be possible to directly sue the FDA if it denies an Orange Book patent listing which comes across as "arbitrary, capricious or not in accordance with law". Andrx argued that the District Court decision could be affirmed here following the APA as the FDA's decision was contrary to law or arbitrary and capricious. But since the complaint did not state any specific counts on which the FDA acted in an arbitrary or capricious manner, the court dismissed any suit against the federal defendants and could

not be appealed as the government was no longer a party to the action. The court however did not close the door on this avenue of relief in future.

This case also brought to attention another problem with the regime wherein Biovail managed to delay the entry of Andrx's generic product by listing a patent claiming a technology that was developed after the marketing of Tiazac which was a consequence of FDA's lack of technical expertise in this area. This provides an example of the abuse of the 30-month stay provision which worked against the generic firm.

Dissenting opinions to the Federal Circuit decision argue that the Federal Circuit has taken a stance that is counter to a previous decision in Mylan Pharmaceuticals Inc. v. Thompson. In that case it held that delisting of a patent does not serve as defense to patent infringement and was not available in a declaratory judgment action in anticipation of an infringement. Moreover, the FDA was being placed in a position of having to address the issue of whether patent listings were correct which the FDA indicated all along that it was not equipped to handle.

Expected effect: An avenue for delisting Orange Book entries by directly suing the FDA for its decision making is provided. This may negatively affect NDA holding firms. The case also brought into question the misuse of the 30 month stay provision to extend their monopoly by making late listing entries in the Orange Book in an attempt to impose thirty month stay's on generic firms seeking FDA approval of their competing product. Generics may be affected positively.

Biotechnology firms show negative significant reactions. Pharmaceuticals and generics don't show any significant reaction. The large negative significant reaction from

biotechnology firms appear interesting and in line with the expectation. Some news events coinciding with this event date for biotechnology firms include, Imclone which became subject to congressional enquiry and was tackling law suits from its share holders alleging that it misled them about one of its drugs, Erbitux's, efficacy following FDA's rejection of Imclone's marketing application on review[40]. Intermune reported positive Phase 3 status on a drug.[41] Removing these firms only mildly reduces the negatives [window (0, 1): CAAR= -3.59%, window (-1, 1): CAAR= -2.86%)] while the generalized sign test remains very significant at .1% and the Patell Z at 5%.

6. In re Buspirone [185 F. Supp. 2d 363 (S.D.N.Y 2002)] Feb 14th 2002:-

Table 2.2.6: In re Buspirone

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.95%	6:12	-0.561	-1.413
(-1,1)	-2.44%	4:14<	-1.101	-2.356*
Firms dropped off 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.42%	7:6	0.495	0.224
(-1,1)	1.07%	9:4	1.170	1.334
Firms dropped off 14	1			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.31%	4:7	-0.680	-0.791
(-1,1)	-1.28%	4:7	-0.696	-0.791
Firms dropped off 16	5			

A set of generic firms brought antitrust action suits alleging that Bristol Myers Squibb (BMS) monopolized the market for its drug, BuSpar, by improperly listing a patent in the Orange book. BMS was accused of attempting to extend its monopoly

[40] 'Imclone stock dives affected by inquiry', Teresa Agovino, 18th Jan 2002, Dow Jones news.
[41] 'Intermune, Inc announces phase 3 IPF study status', 17th Jan 2002, Dow Jones news.

unlawfully to market its buspirone drug in violation of Section one and two of the Sherman Act and abusing many provisions of the Hatch-Waxman Amendments. BMS was unsuccessful in trying to dismiss all the claims. It sought the Noerr-Pennington immunity to antitrust law, which shields efforts to influence the legislature or the executive to take particular action with respect to a law that would produce a restraint in trade or a monopoly[42]. The immunity is however lost if the patent at issue was obtained though knowing and willful fraud that the plaintiff was aware of while bringing subsequent patent suits or if the subsequent infringement suits were a mere sham to interfere with the business of a competitor through use of the governmental process. The court held that the immunity is unavailable to BMS since it applies in situations where the governmental entity makes a decision based on an independent review of the merits of the petition. The FDA however, acts in a ministerial or non-discretionary fashion in the listings that it makes on the Orange Book and so the doctrine was inapplicable. It further held that even if the doctrine was applicable sufficient evidence was present to show that the immunity is lost due to BMS's repeated attempts to stall generics from entering the market.

Expected Effect: The case would encourage small generic drug manufacturers to file antitrust counterclaims if late listings are made by patent holding firms as they could be viewed as an attempt at extending monopoly to stall entry. It might impact firms listing their NDAs on the Orange Book negatively with this course of action available to ANDA

[42] In Eastern Railroad Presidents Conference v. Noerr Motor Freight, Inc. 365 U.S. 127 (1967), the Supreme Court held that "no violation of the Sherman Act can be predicated upon mere attempts to influence passage or enforsement of law."

applicants and lack of consideration for immunity against such an action. This is more so in case they decide to make a later listing.

Biotechnology firms reacted negatively over the (-1, 1) event window which is significant at the 5% level. Pharmaceuticals react positively but it was not statistically significant. Generics reacted negatively but it was not significant. There were no exceptional reactions for any particular firm or coinciding events. The negative significant CAARs for biotechnology firms upholds the possibility of decreased expected net returns to patent holding firms from the decision which apparently discourages late listings to extend monopoly.

7. Apotex v. Thompson [347 F. 3d 1335 (Fed.Cir. 2003)] October 27, 2003:-

Table 2.2.7: Apotex v. Thompson

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-2.02%	3:14<	-1.911$	-2.555*
(-1,1)	-0.31%	10:7	-0.170	0.842
Firms dropped out of 20	3			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.88%	3:11<	-1.280	-1.968*
(-1,1)	-0.18%	7:7	-0.276	0.172
Firms dropped out of 14	0			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.59%	8:7	-0.631	0.487
(-1,1)	0.07%	9:6	-0.083	1.005
Firms dropped out of 17	2			

This case also involves Orange Book listing issues. Apotex here contested FDA's role in listing drugs on the Orange Book. The dispute arose in relation to Apotex's

ANDA pertaining to Smithkline Beecham Corporation's antidepressant drug called Paxil. Smithkline Beecham managed to impose three consecutive 30- month stays on FDA's approval of Apotex's ANDA through its three consecutive sets of late patent listings that enabled extending the protection on its drug. The U.S. District Court for the District of Columbia held that it was lawful for the FDA to list those patents because the Hatch-Waxman Act allowed listing of later-issued patents that had not been obtained at the time that the original NDA was filed with and approved by the FDA. Prior to this Federal Circuit appeal, Smithkline voluntarily requested that the FDA delist the third set of patent listings and thus remove the 30- month stay on the approval of Apotex's ANDA. Taking into account the issues being faced with regard to the 30 month stay provisions, the FDA meanwhile published a new regulation taking the position that the Hatch-Waxman Act intended to allow only one 30-month stay for each ANDA, even where the NDA holder has listed multiple patents for the same NDA. This rule was later incorporated into the 2003 amendments to Hatch-Waxman Act provided in the Medicare Prescription Drug Act. The rule however was not applicable to the current case as the patent information at issue was submitted before the effective date of the new regulation. Although the FDA terminated the third 30- month stay on approval of Apotex's ANDA, it refused to delist the patents in question immediately since the effect of such a change on the right of other ANDA applicants to share the 180-day market exclusivity will have to be taken account of. FDA later issued a guidance document to the industry regarding its interpretation of the 180-day exclusivity when multiple ANDA's are submitted[43]. It clarified that if multiple ANDAs containing a paragraph-four certification to a listed patent for a drug product not challenged under this certification before are submitted on the same day, then

[43] FDA guidance report (July 2003), Link: http://www.fda.gov/CDER/GUIDANCE/5710fnl.htm

the ensuing 180-day exclusivity period is to be shared by all these ANDAs. During this exclusivity period, the FDA may approve other first ANDA applicants pertaining to the listing on that drug product but the newly approved ANDA will get to share only the period left on the exclusivity. The FDA finally approved Apotex's ANDA for a generic version on Paxil on which it was entitled to a share of the 180-day exclusivity period. Apotex however continued with its Federal Circuit appeal to delist the later listed patents since had these later listings not existed, it could have potentially excluded the other ANDAs with which it has to now share the exclusivity period. It was of the view that the FDA has to take up the duty of screening these listings and the district court erred in not ordering FDA to screen these listings. Federal Circuit held that the clear language of the statute does not require the FDA to police the listing process by analyzing whether the patents listed actually claim the subject matter. It also confirmed that though FDA listings can be judicially reviewed as governed by the APA, generic companies would obtain no benefit from this challenge. Divergent opinions were voiced in the Federal Circuit with some alluding to the need for statutory reform since no adequate oversight mechanism seemed to be in place to monitor the activities of private parties listing patents or to resolve disputes that ensued.[44]

Expected Effect: The NDA holders are expected to continue benefiting from this grey area in the statute as it continues to be contested while generics would be hurt as the gap is not closed yet another time.

Biotechnology firms react negatively over the two windows with sign test significance at 5% over the (0, 1) window. Pharmaceuticals also show a slight negative

[44] Derzko (2005), pg. 165

reaction with sign test significance at 5% over the (0, 1) window. The generics don't show any significant reaction over the two windows. The negative reaction of innovative firms may be representative of the mixed reaction from the court especially from dissenting judges indicating the need for reform in this statute. The Medicare Prescription Drug Act's amendment to the Hatch-Waxman Act[45] which was passed in December of the same year didn't change the FDA's ministerial role very much but did bring about statutory changes discouraging improper Orange Book listing issues. This included allowance of only one thirty month stay on an infringement suit against an ANDA applicant so as to discourage late listing during the stay, introducing a declaratory judgment action that a generic company might commence if the firm holding patent rights doesn't file an infringement action within forty five days so as to clarify whether any infringement issues could arise, and permitting an Orange Book patent delisting counterclaim to a paragraph- four infringement lawsuit.[46]

In summary, three out of four cases examining Orange Book listing disputes have been discussed above. Biotechnology firms have reacted with some significance in most cases. Pharmaceutical firms show some significant negative reaction in Apotex v. Thompson. In general from the discussions presented above for the three cases, it appears as though the courts began to recognize the Orange Book listing inconsistencies that were exploited by NDA holding firms and the need for reform. Moves to bring about some sort of reform such as suggesting APA as a judicial avenue to seek delisting of Orange Book listings in Andrx v. Biovail, were received negatively by innovative firms. In Apotex v. Thompson however, the Federal Circuit confirmed that though FDA listings could

[45] Pub. L. No. 108-173, Title XI, 1101, 1102 (codified as amended at 21 U.S.C. 355(j) (2) and (5) (2004)).
[46] Id. at 355 (j) (5) (c) (ii) (I), 355 (j) (5) (c) (ii) (II), 355 (j) (5) (c) (iii) ; A good discussion on the Act also provided by Derzko (2005), pg. 165.

judicially reviewed under APA, the generic companies cannot obtain any benefits from this challenge. It further clarified that the FDA was not required to be put in a position of screen listings as it is beyond its duties as per the statutes. This case highlighted the divergent opinions that existed within the court regarding the role of the FDA and the need for statutory reform to monitor listings. As discussed above, the Medicare Prescription Act had in fact, later amended the statute to provide generic drug applicants with avenues to contest Orange Book listings that they believed to be incorrect. The biotech and pharmaceutical firms returned negative CAARs in the event study pertaining to this case. The debates suggesting need for reform may however, have been instrumental in this negative reaction. In case of In re Buspirone, the courts held that the Noerr-Pennington immunity was unavailable to innovative firms facing anti-trust lawsuits for improper listings on the Orange Book. Biotechs again reacted with a significant negative CAAR. These events seem to imply that changes in the application of Orange Book listing procedures following the decisions of the courts were perceived as being negative to innovative firms. The events mostly turn out insignificant for generic drug makers.

Evergreening related disputes that return significant results:

Orange book listing disputes arose largely because the existing FDA rules on patent listing provided room for interpretation and uncertainty regarding what patents were required to be listed. To some extent this has been remedied by the Medicare Prescription Drug Act's amendments to the Hatch-Waxman Act. As mentioned before, the Orange Book lists all the approved drugs along with the related patent claims. The

FDA requires listed drugs to be approved and determined to be safe and effective. It does not however examine the propriety of patent claims. Due to the uncertainty regarding which patents need to be listed, firms with an approved New Drug Application (NDA) would follow the practice of "evergreening" their patents. The filing of improvement patents relating to the original patents on a drug substance, drug product, or method of using drug is often referred to as "evergreening patents". Approved NDA holding firms also follow the practice of using a series of related patents covering different aspects of the same basic product invention in combination with patent term extensions to unduly prolong the exclusive market period. The Act in general required listing of any patent which claims the drug or the method of using such a drug for which the NDA is submitted. The FDA followed the practice of including both drug substance (ingredients) patents and drug product (formulation and composition) patents as claiming the drug. The FDA regulations however did not clarify whether patents directed to metabolites, polymorphs, intermediate forms of a drug and modes of drug delivery can be appropriately listed. A specific drug substance can sometimes take different crystalline forms, which are referred to as polymorphs. A metabolite refers to anything that is formed during the metabolic process. The regulations were not particularly clear about the correct way of listing patents which claim a drug substance that changes form from the initial to the final stage of the making of a drug product as in the case of polymorphs and metabolites. Such cases discussing listing issues relating to crystalline forms and metabolites of drug substances which were addressed in courts are discussed below.

The Medicare Prescription Drug Act amendments to the Hatch-Waxman Act brought about some essential changes to address evergreening of patents. Drug

manufacturers are no longer allowed to list patents in the FDA Orange Book for drug packaging, drug metabolites, and intermediate forms of a drug. Permitted listings include patents on active ingredients, drug formulations, and uses of a drug. In addition, a more detailed signed attestation accompanying a patent submission is required, and false statements in the attestation could lead to criminal charges. This is expected to significantly reduce opportunities of listing inappropriate patents just for the sake of preventing fair competition from generic drugs.

8. Ben Venue v Novartis [10 F. Supp. 2d 446] June 23rd 1998:-

Table 2.2.8: Ben Venue v. Novartis

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	2.57%	11:6	2.205*	1.554
(-1,1)	3.07%	10:7	1.996*	1.067
Firms dropped out of 20	3			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	1.29%	9:2>	1.761$	2.283*
(-1,1)	0.64%	8:3)	0.741	1.679$
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.54%	5:4	-0.448	0.665
(-1,1)	1.69%	6:3	0.721	1.336
Firms dropped out of 16	7			

The contested issue in this case was whether patents directed to crystalline forms can be properly listed. Ben Venue, a generic company contested Novartis's Orange book listing related to a drug Aredia. Ben Venue had filed an ANDA to manufacture a generic form of Aredia and filed a paragraph-four certification that the patent listing claiming this

drug was uninfringed. Within forty-five days Ben Venue also filed a declaratory judgment action asserting that the patent was improperly listed and did not claim Aredia. Ben Venue's issue here was that the patent in question seemed to cover crystalline forms that include water where as, the listed product Aredia did not contain any water. Novartis argued that the compound covered in the patent is the 'active ingredient' or the 'drug substance' of Aredia. The U.S. District Court for the District of New Jersey finally ruled in favor of Novartis, that crystalline forms can be incorporated in the drug substance aspect of a patent claim, where the drug substance is a component of the drug product. It was not necessary for the patented drug product to appear in the final drug product in order to be listed properly.

Expected Effect: This case seems to positively impact NDA holders as they can list the final product based on a patent on its polymorph drug substance. Generics cannot claim non-infringement or invalidity of these patents in an attempt to enter the market.

Biotechnology firms react positively with Patell test significant at 5% level. Some of this reaction is dominated by Medimmune's drug approval (9%) on day 0. On day -1 PDL increased a lot (12%) from grant of a license[47]. Removing Medimmune and PDL from the selected set of biotech firms, continues to return positive values [window (0, 1): CAAR= 1.99%, window (-1, 1): CAAR= 1.57%] with the same level of significance. Pharmaceuticals also show a positive reaction with Patell test significant at the 10% level and generalized sign test significant at the 5% level over the (0, 1) window. Generic firms

[47] FDA approves Synagis for marketing- Breakthrough preventive treatment for RSV in infants', Dow Jones Reuters business news, 23rd June 1998; ' Protein Design Labs grants a license to Elan', Dow Jones news 23rd June 1998.

react positively over the (-1, 1) window and negatively over the (0, 1) window but neither result is significant.

9. Warner Lambert Co. v. Apotex corp [316 F.3d 1348 (Fed Cir.2003)] January 16th 2003:-

Table 2.2.9: Warner Lambert Co. v. Apotex

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.39%	10:7	0.297	0.874
(-1,1)	-1.09%	8:9	-0.191	-0.097
Firms dropped out of 20	3			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.05%	7:7	0.060	0.018
(-1,1)	-0.96%	3:11<	-1.010	-2.120*
Firms dropped out of 14	0			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	2.14%	8:5	2.122*	0.911
(-1,1)	1.18%	8:5	1.215	0.911
Firms dropped out of 16	3			

In this case, the Federal Circuit addresses the question of whether patents directed to unapproved uses could be listed in the Orange Book. Patent-holders interpreted the listing requirements broadly and listed method of use patents directed to methods of using approved drug products or substances for an unapproved indication. In this case, Warner-Lambert had listed a drug covered by a patent directed to a usage that was unapproved. Warner-Lambert's drug Neurotin(r) had been covered by a patent on a method directed to the approved use of treating epilepsy and a patent directed to the active ingredient, both of which had expired. There remained an unexpired patent directed to the use of the active ingredient in the treatment of an unapproved indication, neurodegenerative diseases. Warner-Lambert listed this patent and Apotex, an ANDA

applicant filed a paragraph four certification. Apotex claimed that its ANDA was indicated for use in the treatment of epilepsy and wouldn't infringe the listed patent. The court agreed that it was not an act of infringement to submit an ANDA for approval to market a drug for a use when neither the drug nor the use is covered by an existing patent, and the patent at issue is for a use not approved under the NDA. By not permitting Warner-Lambert to rely on a method-of-use patent to justify its listing of an unapproved use and establish infringement, the case brought the practice of listing patents for unapproved uses into question.

Expected Effect: The expectation here is that NDA holders would be cautious about their patent listings as the practice of evergreening to keep generic drug applicants out of the market is discouraged. Generics on the other hand benefit from this.

The results reveal no consistent effect on the days surrounding the event day for Biotechnology firms. Some confounding events for biotechnology firms include- Xoma faced drug approval news and receipt of a share of profits in its collaboration with Genentech. Xoma exhibited strong positives on day 0.[48] Transkaryotic Therapies (TKT) faced an FDA rejection for its drug trials for a rare disease, increasing the chance of Genzyme's product in the same area to be the first and only treatments in the USA as FDA rules require only one drug to be approved to treat a rare disease of that sort. Accordingly, TKT reacted very negatively on day -1[49]. After removing these firms, very small insignificant CAARs remained [window (0, 1): CAAR= -0.01%, window (-1, 1): CAAR= 0.36%]

[48] 'Genentech: Sees Raptiva Approval Toward Year-End', Hollister H. Hovey, Dow Jones News, 15th Jan 2003

[49] 'Transkaryotic Therapies shares fall on FDA rejecting Fabry's drug', Dow Jones News, 15th Jan 2003

Pharmaceuticals show some mild negative significant reaction for the (-1, 1) window. In case of generic drug manufacturers, Watson, citing its strong generic and women's health unit's performance, did well on day 0. Removing Watson reduces the reaction from the set of generic drug manufacturing firms considered and makes it insignificant [window (0, 1): CAAR= 0.67%, window (-1, 1): CAAR= -0.14%].[50]

10. Schering Corp. v Geneva Pharms. Inc. [339 F.3d 1373 (Fed Cir. 2003)] August 1st 2003:-

Table 2.2.10: Schering v. Geneva

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.71%	7:10	-0.668	-0.629
(-1,1)	-1.63%	4:13<	-1.090	-2.085*
Firms dropped out of 20	3			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.40%	9:5	0.480	1.211
(-1,1)	-1.83%	2:12<	-1.761$	-2.533*
Firms dropped out of 14	0			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.36%	7:8	-1.394	-0.122
(-1,1)	-2.65%	5:10	-1.466	-1.155
Firms dropped out of 17	2			

In this case the Federal Circuit affirmed a District Court decision that a patent to a pro-drug inherently anticipates the metabolite that is produced by a pro-drug in the body. A pro-drug is an inactive precursor of a drug which becomes active after being ingested and the metabolic process converts it into other compounds with requisite characteristics. The Federal Circuit decision effectively prevents the patenting of metabolites themselves

[50] 'Business Briefs' , Dow Jones News, 16th Jan 2003

in some circumstances. Geneva applied for an ANDA and filed a paragraph-four certification on Schering's listing on its brand drug Claritin. One of its listed patents claimed DCL which was an active metabolite of Claritin (loratadine). Also its patent claim on loratadine had expired. Geneva was of the view that the compound claim covering DCL is invalid because it is anticipated by a patent covering the parent drug, loratadine. The Federal Circuit agreed with this argument. Prior to this case, pioneer pharmaceutical companies could strategically patent and market a pro-drug and the metabolite that is formed from the drug. Accordingly, they could secure patent claims covering the pharmaceutical compositions, pro-drugs and formulations containing the compounds, and treatment methods involving administration of the compounds. They could essentially exclude any competitor seeking to market a pharmaceutical product containing the parent or the metabolite. The Federal Circuit decision essentially clarified that pro-drugs cannot place an economically viable claim on its metabolite since the metabolite is inherently anticipated. Following this decision, a competitor could patent and market an unobvious and unanticipated pro-drug of a metabolite and it wouldn't be infringing as metabolites couldn't be listed.[51]

Expected Effect: The expected effect is negative especially for patenting firms involved in metabolite product patenting. Such patents can be more easily contested and also face easy loss of market share and exclusivity.

Biotechnology firms and pharmaceutical firms reacted negatively with some significant results over the (-1, 1) window. Excluding Schering AG., a pharmaceutical company which reacted exceptionally negatively on days -1 and 0 due to poor profit

[51] De La Rosa (2006). Link: http://law.bepress.com/expresso/eps/1414/

projections and exchange rate issues,[52]doesn't change the CAARs very much [window (0, 1): CAAR= 0.35%, window (-1, 1): CAAR= -1.30%] while retaining sign test significance for the (-1,1) window.

Generics react negatively but not in a significant manner. Much of the reaction is dominated by Dr. Reddy's labs which reported a fall in profits due to low sales of its generic form of Prozac[53]. Removing Dr. Reddy's labs reduces the negatives and the result remains insignificant [window (0, 1): CAAR= -0.63%, window (-1, 1): CAAR= -1.91%].

In summary, the above three cases on evergreening exhibit some reactions in the expected direction for biotechnology firms and pharmaceutical firms. These cases may be of some consequence in this analysis. Changes in regulations regarding metabolites may have been of particular interest to innovative firms since generic drug manufacturing firms became less restricted in finding close substitutes in manufacturing generics. In contrast, allowing crystalline forms to be included in drug substance claims would enable innovative firms to exclude generic drug makers from marketing a different form of the same drug. Innovative drug makers may have found the benefits from this decision to be outweighing any increased listing or regulatory costs. Similarly, disallowing metabolites from being included in patent claims opens up the market for generics to manufacture drugs that produce the same metabolites using substitutes. Following this decision in Schering corp. v. Geneva, innovative firms may have found themselves having lost many benefits from making a broad listing. Finally, in Warner Lambert Co. v. Apotex, the practice of listing drugs for a use that is not covered by a patent for an approved drug is

[52] 'Schering tumbles on FY sales and net profit warning, anemic Q2', Dow Jones news, 31st July 2003
[53] 'Dr. Reddy's Q1 profit falls, Prozac competition hurts', Dow Jones News, 31st July 2003.

also called into question hence discouraging the practice of evergreening. Here again, pharmaceutical firms returned negative cumulative average abnormal returns.

The rest of the cases listed above in table 2.1 did not exhibit very significant reactions by any of the selected groups of firms. The details of these cases and the results obtained are discussed below.

Patent related cases that did not return significant results

1. Diamond v. Chakrabarty [447 U.S. 303] June 16th 1980:-

Table 2.3.1: Diamond v. Chakrabarty

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.87%	6:3	1.327	1.203
(-1,1)	0.76%	4:5	0.893	-0.134
Firms dropped out of 14	5			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	6.40%	1:1	1.996*	0.219
(-1,1)	6.01%	1:1	1.506	0.219
Firms dropped out of 17	15			

The symbols $,*, ** and *** denote statistical significance at the 0.10, 0.05, 0.01 and .001 levels respectively, using a 2-tail test. The symbols (, < or), > etc. correspond to $,* and show the significance and direction of the generalized sign test.

Chakrabarty, a microbiologist working for GE, genetically engineered a bacterium capable of breaking down crude oil. He sought to patent his creation under 35 U.S.C. section 101, providing patents for anyone who "invents or discovers any new and useful process, machine, manufacture or composition of matter, or any improvements thereof". The patent examiner rejected Chakrabarty's application because as per the law living organisms could not be patented. The Patent Office Board of Appeals agreed with the original decision but the Court of Custom and Patent Appeals reversed. Following

this Sidney A. Diamond, then commissioner of Patents and Trademarks, appealed to the Supreme Court. The Supreme Court affirmed and held that a live, human-made micro-organism is patentable subject matter under 35 USCS 101 and constitutes a "manufacture" or "composition of matter" within the meaning of 101. Regarding the scope of the original legislation, the court was of the opinion that the usage of terms like "any manufacture or composition of matter" seems to imply patent law being given a broad scope. Following this argument, the man made bacterium represented a non-naturally occurring manufacture or composition of matter having a distinct character and use which makes it patentable.

Expected Effect: The event expands exclusivity and is expected to positively impact patenting firms especially those involved in patenting man-made biological products.

Since most biotechnology firms were not formed at this time, no data is available to analyze their reactions. Pharmaceuticals react in a mild positive insignificant manner. Most generic firms dropped out as well due to reasons similar to biotechnology firms and exhibited no significant reaction on day 0. Day 1 show's a large positive reaction from KV pharmaceutical (one of the 2 remaining generic companies) which dominates the AR for generics on day 1. While Mylan reacts in a mild negative manner. The effect on generics and biotechnology in all remains inconclusive here.

It is not very surprising that this legally important case did not exhibit any significant effect on biotechnology since at the time of this decision this was a relatively nascent industry. This decision could however be credited for the currently noticeable

growth in biotechnology as it set precedent for the allowance of patenting man-made biological products that biotechnology firms today essentially specialize in.

2. In re Pleuddemann [910 F.2d 823] Aug 3 1990:-

Table 2.3.2: In re Pleuddemann

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.63%	2:6	-0.501	-1.255
(-1,1)	-2.69%	3:5	-1.643	-0.547
Firms dropped out of 20	12			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.32%	5:4	0.489	0.429
(-1,1)	-1.24%	1:8<	-1.826$	-2.239*
Firms dropped out of 14	5			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell Z	Generalized sign Z
(0,1)	-3.52%	2:4	-1.763$	-0.551
(-1,1)	-3.18%	2:4	-1.286	-0.551
Firms dropped out of 17	11			

This appeal followed from a U.S. Patent and Trademark Office (USPTO) Board of Patent Appeal's decision to reject Dr. Edwin Pleuddemann of Dow Corning Corporation's patent application. The U.S. Court of appeals for the Federal Circuit reversed. The decision enabled patenting of "method of using" claims following Pleuddemann's view that the process and method of using claims on his invention should be patentable because articles made by using their new product have superior qualities. The court also explained that process claims can be divided into 'method of making" and "method of using" claims. It was in public interest to permit the appellant to claim the process (of use) as well as the product. The result would be to encourage a detailed

disclosure of methods of using novel composition in order to find support for process claims.

Expected effect: Allowance of patenting the method of using a product could be considered an addition to the patentability domain and exclusivity to patent holders. This may lead to a positive impact on patent holding firms and negative one on generics to the extent that patent holding firms extend their exclusivity by claiming a new process.

Biotechnology firms react negatively over the (0, 1) and (-1, 1) windows. Results from neither window are significant. Pharmaceuticals react negatively over the (-1, 1) window consistent with the case of biotechnology firms. The sign test is significant at the five percent level for this window. The negative response of Pharmaceuticals and Biotechnology firms appear inconsistent. Generics also respond negatively with mild significance dominated by Teva Pharmaceuticals with no particular coinciding news. It can also be noticed that compared to other cases discussed in this study, a larger number of firms drop out of the event study due to lack of sufficient data. These issues make the results ambiguous and nothing conclusive is being said here.

3. Warner Jenkinson [520 U.S. 17] March 3rd 1997:-

Table 2.3.3: Warner Jenkinson

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.19%	6:10	-0.502	-0.632
(-1,1)	-0.68%	8:8	0.088	0.373
Firms dropped out of 20	4			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.33%	3:8	-0.321	-1.354
(-1,1)	-1.24%	3:8	-1.561	-1.354
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.15%	4:5	0.100	-0.178
(-1,1)	1.49%	7:2)	0.950	1.825$
Firms dropped out of 16	7			

As discussed above in the outline on the Festo (Federal Circuit) decision, the Supreme Court's decision in Warner Jenkinson laid some ground rules which were to be taken account of by the Federal Circuit in making its decision. In the Warner Jenkinson decision, the Supreme Court essentially had to address the issue of the uncertainty that existed in the allowable range of equivalents to an invention, in applying the doctrine of equivalents. The Court held that - 1. Doctrine of equivalents is applicable to individual elements of a claim not to the whole invention. 2. Although prosecution history estoppel is available, if the patent holder demonstrates that the reason for amendment was unrelated to patentability, then the doctrine of equivalents is available to the patent holder.

Expected Effect: This case appears to enhance the rights of patent holders since the Supreme Court was seen as having reconciled its precedent in the area of the Doctrine of

Equivalents which was one of the issues of ambiguity. Through this decision the Supreme Court affirmed the existence of the doctrine against a challenge that would have nearly defined it away. It also established that doctrine of equivalence should be applied to individual claims and adopted an interpretation of prosecution history estoppel that was less severe. Beyond this it left it up to the Federal Circuit to determine the correct tests for equivalence reaffirming the Federal Circuit's role as a more specialized body in this area. The Federal Circuit did end up establishing some tests in a following decision in Festo v. SMC.

Biotechnology firms show some negative reaction over the two windows and so do the Pharmaceuticals. Generics show a positive reaction over the (-1, 1) window and a small negative one over the (0, 1) window. None of them however turn out very significant. Mild negative reaction from biotechnology and pharmaceuticals may represent the losses they face from cost increasing effect of this case.

4. Festo – Supreme Court [535 U.S. 722] May 28th 2002:-

Table 2.3.4: Festo – Supreme Court

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.24%	11:7	.272	1.039
(-1,1)	-0.68%	5:13(	-0.490	-1.791$
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.88%	7:6	1.409	0.318
(-1,1)	-1.34%	3:10(	-1.758$	-1.901$
Firms dropped out of 14	1			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.59%	8:4	0.372	1.320
(-1,1)	0.51%	7:5	0.185	0.742
Firms dropped out of 16	4			

The two issues discussed by the Federal Circuit in this case previously were addressed here by the Supreme Court. The Supreme Court agreed that any claim amendment narrowing the scope of a patent gave rise to prosecution history estoppel regardless of the reason for amendment. It however reversed the absolute bar restriction and adopted more flexibility. The patentee may now show that "at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." A narrowing amendment need not make the claim foolproof in finding another equivalent. Following this decision if the patentees can show that the equivalent was unforeseeable at the time of application or if the patentee could not be expected to describe the equivalent, then the doctrine of equivalents may become applicable. The Supreme Court decision, in effect,

seems to have endorsed the Federal Circuit decision while modifying the complete bar to apply a flexible bar in determining equivalents to an invention.

Expected effect: The Supreme Court decision may have been more favorable to patentees since they could now re-evaluate their patents scope and press claims that may have been barred previously. Lowrie and Topper (2002) also point out that the Supreme Court decision on one hand enables patent owners to reevaluate the scope of their patents and press claims that may have been thought barred under the prosecution history estoppel. On the other hand, it may also raise the time cost and uncertainty associated with patent litigation as additional layers of hearings may ensue in order to determine whether the patentee has met with all the patenting requirements under the flexible standards or the prosecution history estoppel is applicable.

Biotechnology firms react very mildly over the two windows neither of which is significant even after taking account of coinciding news for some firms. Biogen's Psoriasis drug was approved by the FDA which caused it to soar in value (window (-1, 1) CAR= 25%)[54]. A competing firm in Psoriasis, Xoma was viewed favorably following Biogen's drug approval in an industry facing tight FDA regulation in approval at this point (window (-1,1) CAR= 6%)[55]. Removing these firms from the selected biotechnology group raises the negatives over (-1, 1) window [window (0, 1): CAAR= 0.70%, window (-1, 1): CAAR: -2.73%] with only a slight improvement in significance. Pharmaceuticals react negatively over the (-1, 1) window which is significant only at the 10% level. Much of this reaction seems to be dominated by GSK which also happened to

[54] 'Sign of Anxiety', Robert Teitelman, Dow Jones News, 29th May 2002.
[55] 'Biogen Climbs as FDA Approves Key Drug', Dow jones News, 28th May 2002; 'FDA panel recommends Approval for Psoriasis Drug', Andrew Pollack, Dow Jones news, May 24th 2002

lose patent protection on one of its drugs [window (-1, 1) CAR= -5%)[56]. Removing GSK maintains negatives from Pharmaceutical firms [window (0, 1): CAAR= 0.72%, window (-1, 1): CAAR= -1.01%] but doesn't improve the significance over the windows very much. Although the negative reaction from pharmaceuticals and biotechnology seems to follow the argument of strengthened patents decreasing IP domain and increasing costs of innovation, their reaction over the (0, 1) window remains slightly positive and insignificant. This might follow from the fact that the eventual effect is considered uncertain by the patent holders themselves. Generics don't react as much to the event either.

<u>FDA and Regulatory environment related issues that returned insignificant results:</u>

<u>Hatch-Waxman: 180-day market exclusivity and some related cases</u>

5. Purepac Pharm co. v Friedman [162 F.3d 1201 (D.C.Cir 1998)] Dec 29th 1998:-

Table 2.3.5: Purepac Pham co. v. Friedman

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-3.19%	4:14<	-2.174*	-2.108*
(-1,1)	-1.58%	8:10	-0.433	-0.220
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.88%	7:4	1.100	1.049
(-1,1)	0.71%	6:5	0.717	0.445
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-0.74%	4:5	-0.241	-0.181
(-1,1)	1.18%	5:4	1.281	0.487
Firms dropped out of 16	7			

[56] "Drug Firms Stalked by copycats", Cliff Feltman, Dow Jones news, May 28th 2002

Purepac Pharmaceutical Co. which was a generic drug manufacturing firm brought this case against the FDA to the U.S. Court of Appeals for the District of Columbia Circuit. Purepac had filed an ANDA containing a paragraph-four certification for a branded drug sold by Roche Laboratories. It was the second to file an ANDA application. The first applicant TorPharm, was not sued and could avail itself of the 180-day exclusivity from the date when it chooses to first commercially market its product. Purepac was allowed to enter the market only after the expiration of this period. Purepac essentially posed the question "must an ANDA applicant be subjected to patent infringement action in order to obtain a 180-day period of exclusivity?" Purepac argued that TorPharm had to be sued in order to avail itself of this exclusivity. The timing of the oral hearing of this case coincided with the FDA's publication of its "Guidance for industry, 180-Day Generic Drug Exclusivity under the Hatch-Waxman Amendments to the Federal, Food Drug and Cosmetic Act" with the purpose of providing the industry information as to how it is applying the 180-day generic drug exclusivity provisions. The guidance addressed the elimination of the "successful defense" requirement following Mova and makes the language of the regulation consistent with the statute. Purepac however argued that Mova in essence removed "successful" from the "successful defense" requirement in the regulation. It still required that a suit be brought against the generic applicant for it to avail itself of the 180-day exclusivity period. The court did not find this persuasive and followed FDA's guidance rules in its decision. The D.C. Circuit confirmed that the first generic applicant need not be sued for patent infringement to avail of the 180-day exclusivity. This made the ruling more consistent with the statute.

Expected effect: The case reaffirms the decision in Mova enabling the generic firm that is first- to-file to avail itself of the 180-day exclusivity. The expected effect here is similar to Mova with generic drug manufacturing firms racing to file first as they need not be sued to avail themselves of the 180-day exclusivity. Patenting firms as discussed before could enter into blocking coalitions with some generic firms so as to protect some of their market share however this would have to be done at the expense of paying large patent settlement amounts to the generic challenger.

Pharmaceuticals in sum don't react much over the two windows possible since this effect was taken into account following the decision in Mova. Generics react mildly positively but with no significance. Biotechnology firms react negatively over the two windows which is significant over the (0, 1) window at the 5% level. Some of the stocks however seemed volatile around this event period Abgenix exhibited an exceptionally positive cumulative abnormal return value (10%). A possible explanation is the news of collaboration agreement between Abgenix and Centocor in cardiovascular disease research which was received positively[57]. Removing Abgenix alters CAARs to some extent [window (0, 1): CAAR= -2.52%, window (-1, 1): CAAR= -1.41%] but the results become insignificant. Among generics, Mylan reported drug approval related news. On removing Mylan the day 1 negative decreases and the values in the windows become even smaller and insignificant [window (0, 1): CAAR= -0.48%, window (-1, 1): CAAR= 0.67%].[58]

[57] 'Abgenix signs research agreement with Centocor', Dow Jones news, 28th Dec 1998
[58] 'FDA approves Mylan's generic epilepsy capsules', Dow jones news, 30th Dec 1998; 'Nightly Business report', Paul Kangas, Susie Gharib, Dow Jones news, 30th Dec 1998;

6. Apotex v. Shalala [53 F. Supp 2d 454 (D.D.C. 1999)] June 16th 1999:-

Table 2.3.6: Apotex v. Shalala

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.00%	9:9	0.369	0.333
(-1,1)	1.90%	11:7	1.472	1.278
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.47%	8:3	0.603	1.597
(-1,1)	1.03%	8:3	1.019	1.597
Firms dropped out of 14	3			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	-1.13%	4:5	-0.639	-0.147
(-1,1)	-0.23%	4:5	-0.460	-0.147
Firms dropped out of 16	7			

As per the statute the first generic applicant to file an ANDA containing a paragraph 4 certification is awarded 180 days of marketing exclusivity during which the FDA may not approve other ANDAs with a paragraph 4 certification for the same drug product. In this case Glaxo sold three products of different dosage forms, 2 of which were prescription drugs while the third one was an OTC drug. All three of these products are listed separately in the Orange Book. Genpharm was the first to get an approval on its ANDA for the prescription forms of this drug following a paragraph 4 filing. Novopharm was the first to file a paragraph 4 certification on the OTC product. Apotex however sought immediate approval of its application on the OTC form as well based on its theory that FDA may not grant exclusivity periods for ANDA applications that concern the same patents involved in previously- approved drugs of different strengths. The D.C. circuit addressed this question of whether different dosages of a drug are eligible for separate

180-day exclusivity periods. The district court held that separate exclusivity periods for separate drug-strengths is consistent with the statute. Each drug-strength is listed separately on the Orange book so first paragraph 4 certification on each of the listing is eligible for 180-day exclusivity. For similar reasons, tablet forms and capsule forms of the same drug are eligible for separate 180-day exclusivity.

Expected Effect: This is also a case related to the180-day exclusivity provision and similar in some regards to Mova v. Shalala. By the time of the hearing in Apotex v. Shalala, Mova's decision of 180-day exclusivity to the generic firm that is first to file was established. Following the decision in Apotex v. Shalala, as separate dosage forms can lead to separate 180-day exclusivity periods, extension of the exclusivity period to more generics which vie to file ANDAs on different dosage forms listed separately in the Orange Book by patenting firms that apply for NDA (New Drug Applications) may be enabled. The patenting firms might have to deal with an increased number of generics entering each of their markets that were represented by different dosage forms and trying to share their returns from that market. At the same time this decision may have the effect of keeping the rest of the generics from entering the market sooner, as a duopoly like situation would ensue in each of the markets for sometime before it is freed up for entry by any generic drug manufacturer increasing competition.

The results show not much reaction from any of the firms on this event day. While biotechnology firms don't react, pharmaceuticals show a mild positive reaction and generics a mild negative none of which are significant.

Orange Book listing litigation procedure and related disputes that returned insignificant results:

7. Mylan vs. Thompson [268 F.3d 1323] Oct 12th 2001:-

Table 2.3.7: Mylan v. Thompson

Biotechnology firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.61%	10:8	0.294	0.490
(-1,1)	0.76%	10:8	0.375	0.490
Firms dropped out of 20	2			

Pharmaceutical drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	1.17%	9:4	1.518	1.328
(-1,1)	-0.17%	4:9	-0.221	-1.446
Firms dropped out of 14	1			

Generic drug manufacturing firms

Event	CAAR	Positive: Negative	Patell test	Generalized sign test
(0,1)	0.08%	2:9(	-0.882	-1.906$
(-1,1)	0.08%	2:9(	-0.720	-1.906$
Firms dropped out of 16	5			

It is understood that listing of a patent in the Orange book is essential in bringing a patent infringement charge by an NDA holder. In this case Mylan sought declaratory relief arguing that the NDA's patent was improperly listed and delisting of a patent should serve as defense to a possible patent infringement suit. The Federal Circuit however, held that delisting of a patent does not serve as defense to patent infringement and is not available in a declaratory judgment action in anticipation of an infringement. This was deemed to act as a private enforcement of the Federal Food Drug and Cosmetic Act which was unavailable under the Hatch-Waxman Act. Further, the Orange Book was controlled by the FDA with no bearing to the validity of a patent.

Expected affect: Drug patenting firms like pharmaceuticals and biotechnology firms may react positively if challenging their listing in anticipation of infringement charges is unavailable for generics.

From the results it appears that the decision doesn't incite much reaction from the firms. Biotechnology firms react in sum mildly positively for the two windows. Pharmaceuticals also react positively but it doesn't turn out very significant. Generics don't react much. A look at the individual stocks however shows that they are pretty volatile around this event period and tend to cancel each other out leading to ambiguity about the end effect.

2.6 Conclusion

In summary, of the patent related cases, the Festo case at the Federal Circuit and In re Brana seem to evoke relatively more response from the Pharmaceutical and Biotech firms. Generic drug manufacturers don't seem to show much reaction in most cases. Table 2.4 (below) gives a summary table on the reaction of biotechnology firms and pharmaceuticals over the (0, 1) and (-1, 1) windows. Patent related cases seem to support the possibility of strengthening patent rights leading to significant increases in the costs of innovation. As seen in case of In re Brana, the court in allowing early patenting was of the view that requiring firms to conduct successful second stage tests in order to claim utility in a patenting sense was a disincentive to research as it imposes large costs on patenting. However, the reaction of patenting firms in the event studies seems to follow the anti- commons arguments implying that early patenting may create blocking positions

in conducting research and might prove expensive as firms involve in expensive licensing agreements to work around the reduction in public domain. Festo's Federal Circuit case seemed on the other hand to have expanded the prosecution history estoppel by creating an absolute bar to coverage for all equivalents to an amended claim. This puts restrictions on the usage of the doctrine of equivalents in an infringement claim. The patenting firms however react positively in the event studies implying the possibility of a narrowing patent protection leading to a decrease in cost of innovation and opening of new areas for future research.

Cases relating to the FDA and the regulatory environment through statutory provisions like 180-day exclusivity, Orange Book listing issues and evergreening cases that have been considered here, show varying responses from patenting firms over the two windows. The180-day exclusivity related cases and the cases based on evergreening by patenting firms seem to follow the expectations even after taking into account some of the coinciding events faced by firms. Three of the analyzed cases on Orange Book listing procedure disputes incite a response from patenting firms, however one of these three (Apotex v. Thompson) doesn't follow the expectation.

Of the 180-day exclusivity related cases, pharmaceutical firms show significant negative reactions for the Mova cases. Biotechnology firms also reacted significantly negatively to Mylan v. Shalala. These cases were instrumental in reducing exclusivity to firms marketing new drugs. The results seem to imply a pro- exclusivity behavior from the patenting firms or the New Drug Applicants which includes mostly pharmaceuticals and biotechnology firms. In these cases generic drug manufacturers have reacted

insignificantly over the two windows. The nature of these cases has been mainly to clear ambiguities in statutes.

The Orange Book listing related cases also incite much less reaction from generics over the two windows. Biotechnology firms show a strong negative reaction in case of Andrx v. Biovail and in In re buspirone. Both biotechnology and pharmaceutical firms react negatively to the decision in case of Apotex v. Thompson. The results here seem to imply that changes in the application of Orange Book listing procedures following the decisions of the courts were perceived as being negative to innovative firms.

With regard to the cases on evergreening discussed in this study, Schering Corp v. Geneva made it harder for patenting firms to evergreen their patents and to acquire extensions on their patents through Orange Book listings. This case led to negative abnormal returns for patenting firms which again seems in agreement with the possibility of innovative firms losing their incentives from not being allowed to make broad listings. Ben Venue v. Novartis which allowed NDA holders to list crystalline forms in the drug substance aspect of a patent claim was received positively by patenting firms. Finally, Warner Lambert Co. v. Apotex Corp. brought to question the practice of listing unapproved uses for an approved drug. Pharmaceutical firms reacted negatively to the court's decision discouraging this practice. Again most generic drug manufacturers didn't react very significantly even after taking account of news events.

A stronger regulatory environment which limits the range of listings of innovative firms or eases entry of generic drug makers seems to be perceived negatively by the patent holding innovative firms. Biotechnology and pharmaceutical firms seem to react

negatively on instances where ambiguities about the 180-day exclusivity provisions to generic drug manufacturers are cleared or when evergreening is discouraged. The results lead to the possible inference that biotechnology firms and pharmaceuticals are negatively affected by any provisions negatively affecting exclusivity offered by the regulatory environment surrounding drug approval. Revenue loss due to competition from generic drug manufacturers following changes in the regulatory environment seems to be of more consequence to new drug applicants than any benefits that may have ensued in the form of reduced licensing costs or transactions costs in their research process. With respect to the patenting cases on the other hand, competition among the innovative firms may be of more relevance. Loss of intellectual property domain may be of more relevance to innovative firms than increased profits from a given set of patents. The lack of any reaction from generic drug manufacturing firms in the above analysis may be a less surprising result especially in cases where there has been a reduction on entry restrictions as this is reflective of the markets becoming more competitive and no supernormal returns being appropriated by any of them.

Though the cases considered here are not exhaustive, in general there have been more instances where changes in regulation have lead to a negative CAAR. Most of these decisions regarding regulation appear to have reduced exclusivity provided to innovative firms either by limiting Orange Book listings or by easing the process of generic entry. This may also be interpreted as more instances where the incentives to innovative firms are reduced. Following the theoretical model laid out initially in the chapter, their producer surplus could be negatively impacted implying that fewer new inventions are expected. Ben Venue v. Novartis was the one case where the court allowed innovative

firms to make a broad listing and a corresponding positive CAAR was observed for biotechnology and pharmaceutical firms. Nothing very conclusive can be said about the effect of an increased exclusivity on new inventions. However, four cases for pharmaceutical firms[59] and four out of five cases for biotechnology firms[60] which were expected to reduce exclusivity were received negatively. This leads to the conclusion that changes in regulation since the passage of Hatch-Waxman Act to amendments introduced to the Act in 2003 have been mostly negative to innovative firms. In most instances, they have hurt their returns more than any benefits that may have ensued from reduction in their listing, licensing or transactions costs.

Based on the above discussion and the results obtained, the cases for which biotechnology and pharmaceutical firms considered here returned significant results are further analyzed in the next chapter to examine the effect on the R&D of these firms, following changes to their returns as shown by the event studies. Generic drug manufacturing firms however are not examined further due to lack of any significant reaction from them in the current study and also since their research and development expenses may be less representative of innovative drug research but done with the intent of replication.

[59] Mova v. Shalala (District level), Mova v. Shalala (Federal Circuit), Warner Lambert v. Apotex, and Schering Corp. v. Geneva returned negative CAAR.
[60] Mylan v. Shalala, Andrx v. Biovail, In re Buspirone, Schering Corp v. Geneva returned a negative CAAR as expected but Festo (Federal Circuit) returned a positive CAAR though expected to be negative.

Table 2.4: Summary of CAARs over (0,1) and (-1,1) windows for a set of biotechnology and pharmaceutical firms

Cases/ Windows		Biotech			Pharmaceutical		
		CAAR	**Patell Z**	**Generalized Sign Z**	**CAAR**	**Patell Z**	**Generalized Sign Z**
	Patent cases						
1	Diamond v Chakrabarty						
	Days (0,1)				0.87%	1.327	1.203
	Days(-1,1)				0.76%	0.893	-0.134
2	In Re Pleuddemann						
	Days (0,1)	-0.63%	-0.501	-1.255	0.32%	0.489	0.429
	Days(-1,1)	-2.69%	-1.643	-0.547	-1.24%	-1.826$	-2.239*
3	In Re Brana +						
	Days (0,1)	0.06%	-0.985	-0.857	-2.05%	-4.002***	-2.575*
	Days(-1,1)	-0.61%	-0.982	-0.857	-3.43%	-5.372***	-3.179**
4	Warner Jenkinson						
	Days (0,1)	-1.19%	-0.502	-0.632	-0.33%	-0.321	-1.354
	Days(-1,1)	-0.68%	0.088	0.373	-1.24%	-1.561	-1.354
5a	Festo 1 --						
	Days (0,1)	3.66%	1.691$	3.124**	0.86%	0.969	0.693
	Days(-1,1)	5.15%	2.031*	2.652**	1.80%	1.527	1.848$
5b	Festo 2						
	Days (0,1)	0.24%	0.272	1.039	0.88%	1.409	0.318
	Days(-1,1)	-0.68%	-0.490	-1.791$	-1.34%	-1.758$	-1.901$
	Hatch-Waxman 180- market exclusivity cases						
6a	Mova v. Shalala 1 --						
	Days (0,1)	-1.25%	-0.975	-1.653$	-1.76%	-2.902**	-1.979*
	Days (-1,1)	-0.23%	0.118	-0.649	-0.12%	-0.123	-1.375
6b	Mova v. Shalala 2 --						
	Days (0,1)	-0.14%	0.063	0.032	-2.75%	-3.636***	-3.136**
	Days (-1,1)	-0.74%	-0.634	-0.941	-2.84%	-3.110***	-3.136**
7	Purepac v. Friedman						
	Days (0,1)	-3.19%	-2.174*	-2.108*	0.88%	1.100	1.049
	Days (-1,1)	-1.58%	-0.433	-0.220	0.71%	0.717	0.445
8	Apotex v. Shalala						
	Days (0,1)	0.00%	0.369	0.333	0.47%	0.294	1.597
	Days (-1,1)	1.90%	1.472	1.278	1.03%	0.525	1.597
9	Mylan v. Shalala --						
	Days (0,1)	-4.82%	-3.397***	-2.630**	-0.24%	-0.386	-0.208
	Days (-1,1)	-5.41%	-2.811**	-2.630**	-1.36%	-1.410	-0.811

+ increase exclusivity, -- decrease exclusivity

Table 2.4: Summary of CAARs over (0,1) and (-1,1) windows for a set of biotechnology and pharmaceutical firms (cont.)

Cases/ Windows		Biotech			Pharmaceutical		
		CAAR	**Patell Z**	**Generalized Sign Z**	**CAAR**	**Patell Z**	**Generalized Sign Z**
	Orange Book Cases						
10	Mylan v. Thompson						
	Days (0,1)	0.61%	0.294	0.490	1.17%	0.651	1.328
	Days(-1,1)	0.76%	0.375	0.490	-0.17%	-0.075	-1.446
11	Andrx v. Biovail --						
	Days (0,1)	-3.98%	-2.894**	-3.308***	-0.11%	-0.091	-0.307
	Days(-1,1)	-3.65%	-2.177*	-2.365*	-0.47%	-0.482	-0.861
12	In Re Buspirone --						
	Days (0,1)	-0.95%	-0.561	-1.413	0.42%	0.495	0.224
	Days (-1,1)	-2.44%	-1.101	-2.356*	1.07%	1.170	1.334
13	Apotex v. Thompson +						
	Days (0,1)	-2.02%	-1.911$	-2.555*	-0.88%	-1.280	-1.968*
	Days(-1,1)	-0.31%	-0.170	0.842	-0.18%	-0.276	0.172
	Evergreening						
14	Benvenue v. Novartis +						
	Days (0,1)	2.57%	2.205*	1.554	1.29%	1.761$	2.283*
	Days(-1,1)	3.07%	1.996*	1.067	0.64%	0.741	1.679$
15	Warner Lambert v. Apotex --						
	Days (0,1)	0.39%	0.297	0.874	0.05%	0.060	0.018
	Days(-1,1)	-1.09%	-0.191	-0.097	-0.96%	-1.010	-2.120*
16	Schering v. Geneva --						
	Days (0,1)	-0.71%	-0.262	-0.629	0.40%	0.480	1.211
	Days (-1,1)	-1.63%	-0.493	-2.085*	-1.83%	-1.761$	-2.533*

+ increase exclusivity, -- decrease exclusivity

2.7 Appendix A

Table A: Biotech top-20 (SIC 2836)

1	AMGEN INC
2	GENENTECH INC
3	CHIRON CORP
4	SERONO S A -ADR
5	BIOGEN INC
6	MEDIMMUNE INC
7	GENZYME CORP
8	GILEAD SCIENCES INC
9	IMMUNEX CORP
10	CORIXA CORP
11	CENTOCOR INC
12	IMCLONE SYSTEMS INC
13	PROTEIN DESIGN LABS INC
14	XOMA LTD
15	ABGENIX INC
16	NEUROCRINE BIOSCIENCES INC
17	MEDAREX INC
18	CELL GENESYS INC
19	INTERMUNE INC
20	TRANSKARYOTIC THERAPIES INC

Table B: Pharmaceutical top-15 (SIC 2834)

1	JOHNSON & JOHNSON
2	MERCK & CO
3	PFIZER INC
4	BRISTOL MYERS SQUIBB
5	AVENTIS SA -ADR
6	GLAXOSMITHKLINE PLC -ADR
7	WYETH
8	ABBOTT LABORATORIES
9	ROCHE HOLDINGS LTD -ADR
10	NOVARTIS AG -ADR
11	LILLY (ELI) & CO
12	ASTRAZENECA PLC -ADR
13	SCHERING-PLOUGH
14	SCHERING AG -ADR
15	SANOFI AVENTIS

Table C: Generics 17 firms (SIC 2834)

1	MYLAN LABORATORIES
2	PAR PHARMACEUTICAL COS INC
3	BARR PHARMACEUTICALS INC
4	IVAX CORP
5	HI TECH PHARMACAL CO INC
6	INTERPHARM HOLDINGS INC[61]
7	WATSON PHARMACEUTICALS INC
8	CARACO PHARMACEUTICAL LABS
9	GENVEC INC
10	SERACARE LIFE SCIENCES INC
11	PRO PHARMACEUTICALS INC
12	ABLE LABORATORIES INC
13	EON LABS INC
14	IMPAX LABORATORIES INC
15	K V PHARMACEUTICAL -CL A
16	TEVA PHARM INDS -ADR
17	DR REDDYS LABS LTD -ADR

[61] Formed on May 30th 2003 through an acquisition by ATEC group inc., prior to which it was an IT firm. So for events prior to this day the firm has been excluded from the set.

CHAPTER 3

Analyzing the effect of changes in patent law and regulation on R&D expenditure

Using the event study methodology presented in chapter 2, events causing a large and significant market reaction were noted. In this chapter, results from the event study are used to examine research and development behavior of the firms. In what follows, I take the study a step further by examining how the R&D expenditures of these firms react following these events of interest and draw inferences on their possible effects.

3.1 Introduction

Both the Pharmaceutical and Biotechnology industries invest large sums in research and development of new drugs. As figures 3.1 and 3.2 indicate, R&D expenses in these industries have been steadily rising. In their studies analyzing drug development costs, Grabowski, Vernon and Dimasi[62] find the average drug development and introduction costs to be rising along with the time periods involved in the clinical trial process and regulatory approval for drug introduction. Along with rising R&D expenses the drug industry has been facing constant reform. Pharmaceutical and biotechnology industries are different from other research intensive industries in that research in these industries not only depends on the patent environment but also on the regulatory environment and the role that the FDA plays in approving drugs and supervising them as they enter the market. Ramanathan (1999) showed that approval of a drug by the FDA creates significant value for pharmaceutical firms in comparison with the acquisition of patents.

[62] Grabowski, Vernon, and Di Masi (2002) pg. 11-29; Grabowski and Vernon (1994) pg. 383-406; Dimasi, et al., (1991) pg. 107-142

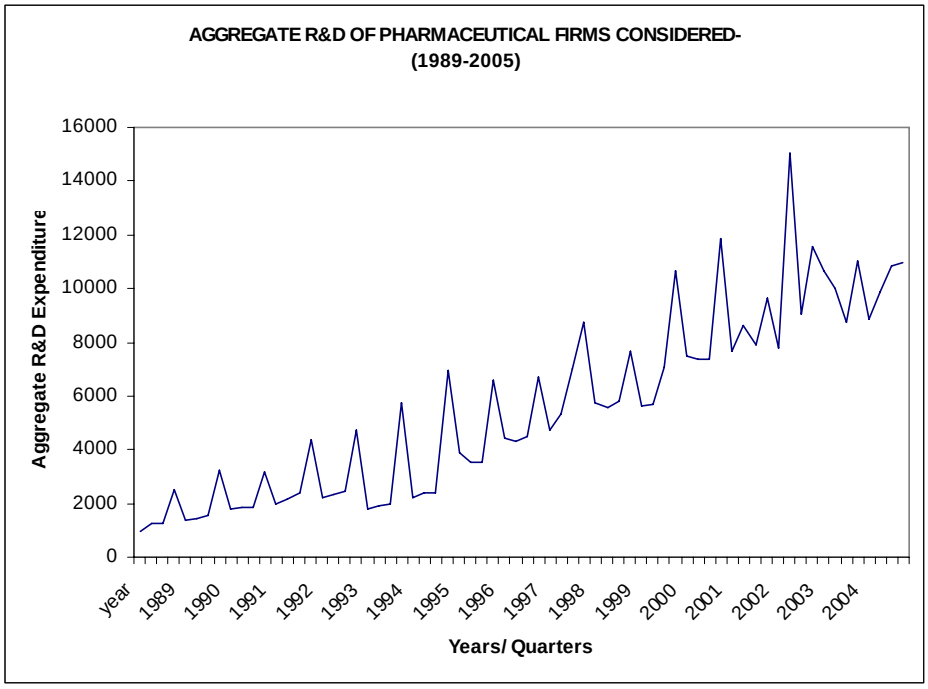
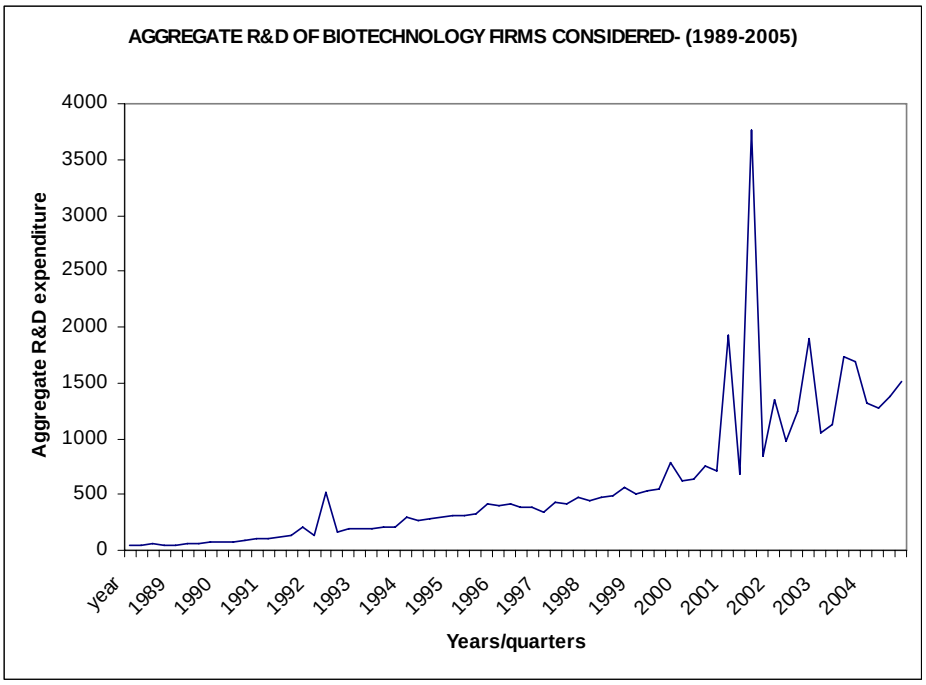


FIGURE 3.1: Aggregate quarterly R&D expenses of 11 Pharmaceutical firms considered in this study over 1989-2005.



Notes: 1. The big spike in R&D on 2002 Quarter 3 is dominated by Amgen which wrote off a huge amount of in-process R&D following its acquisition of Immunex in this quarter (July 2002)

2. 2004 Q3 spike dominated by Amgen and possibly due to Tularik acquisition and write off (Aug 13 2004)

3. 2003 Q4 spike dominated by Biogen. It merged with Idec on Nov 12 2003

4. 2002 Q1spike dominated by Medimmune. It acquired Aviron (Jan 10th 2003)

5. 2003 Q1dominated by Gilead. It acquired Triangle pharmaceuticals Jan 2003 and wrote off huge sum as in-process R&D

FIGURE 3.2: Aggregate quarterly R&D expenses of 14 Biotechnology firms considered in this study over 1989-2005.

One of the major reforms that firms pursuing discovery and development of new drugs have faced is the Hatch-Waxman Act of 1984. The Act was characterized as enabling increased generic competition coupled with an extension of the patent life for patent holding research firms. This was considered to be a compromise between the generic drug manufacturers and research based drug manufacturing firms. On one hand, the Act eased the process of entry of generics; on the other, it extended the patent life of drugs produced by pioneer firms which was expected to keep future research attractive and profitable. Several studies have analyzed the effect of this act on the drug research industry as already discussed

in chapter 1[63]. As per these studies, the effect of the Hatch-Waxman reforms,particularly on research-based industries, have been a near trade-off. As also mentioned in chapter 1 following the passage of this Act various loopholes in the statutes surfaced and were addressed by the courts. Some of the issues were later resolved through the Medicare Prescription Drug Act reforms to the Hatch-Waxman Act in 2003. Some of the issues addressed by the courts were discussed in the previous chapter and cases which significantly altered the returns of research intensive firms were determined and analyzed.

In this chapter, the effect on R&D of these marginal changes in exclusivity is analyzed. Marginal changes in exclusivity are reflected by precedent-setting legal decisions on patents or regulation, since the passage of Hatch-Waxman Act to the Medicare Prescription Drug Act. Though statutory changes establish new norms that industries face, the interpretations of regulations as determined by precedent-setting cases through litigation may play a crucial role in affecting the incentives of drug research and development firms.

3.2 Estimation of effect on R&D from changes in patent and regulatory environment for biotechnology and pharmaceuticals firms

Simple panel data estimation is conducted to analyze the effect of changes in regulatory and patent environment on research and development expenditures of a set of pharmaceutical and biotechnology firms over a period of time. This is done by regressing research and development expenditures of the firms in the two industries that returned statistically significant Cumulative Average Abnormal Returns (CAARs) following the events of interest, on case dummy variables defined to take the value 0 until the quarter prior

[63] Grabowski and Vernon (1986), Joglekar and Patterson (1986), Proctor (1989) etc.

to the event quarter, and 1 from the event quarter onwards. The regression equation used in the estimation is given as follows:

$$RD_{it} = (Case\_k)_t + Sales_{it} + t \quad (3.1)$$

Where RD_{it}= Research and Development Expenditure per firm per time period

$(Case\_k)_t$= ('k' being the case number from Table 2.1) Takes value

=0 till the quarter before the patent or regulatory change took place

(also referred to as the event quarter)

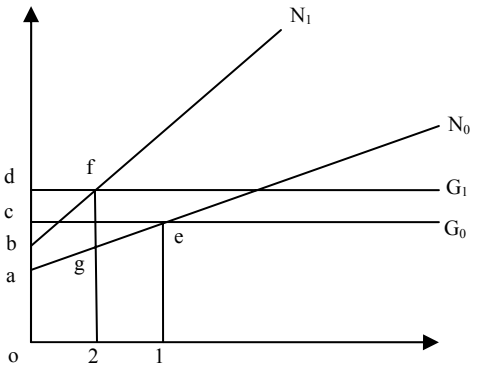
=1 from the event quarter to the end of the time series for that firm.

$Sales_{it}$= Sales per firm per time period

t= Trend

A trend variable is added to capture the trend in R&D for the two industries considered. Sales of each firm considered are also added to take account of size of firms. The $(Case\_k)_t$ variable is modeled in a manner which assumes a constant change post event. Seven such variables have been used in estimating R&D for the set of biotechnology and pharmaceutical firms, corresponding to the cases that returned statistically significant CAARs when analyzed in the event studies in chapter two. Coefficients on the case dummies will inform us of any significant increases or decreases in the research and development expenses around the event quarters. The change in research and development expenses as implied by these coefficients, are then analyzed in conjunction with the CAARs that were obtained on that case from the event studies of chapter two. This allows us to draw an inference on the relation between the observed change in the market valuation of firms and the change in research and development expenses from the above estimation.

Cumulative Abnormal Returns (CARs) are taken in this study to act as a proxy measure representing the changes in research incentives of firms following patent and regulatory changes. From the theoretical argument set out in chapter two, the CAR values are representative of the change in producer surplus which is a combination of both the revenue-change aspect and the cost-change aspect so that if the expected changes in the revenue are greater than the change in cost of innovation, the CAR would be positive and vice versa. Research and development expenses of firms are a component of the costs faced by them in their process of innovation. Changes in patent and regulatory environment have this two-fold effect on revenues and costs as discussed in the model developed in chapter two. In the above estimation equation, by regressing R&D on case dummies, inferences can be drawn about the change in firm research activity around the event quarters. Estimation of the above equation may yield a positive or a negative coefficient on the $(Case\_k)_t$ variables. A positive coefficient in association with a positive CAAR (from chapter two) would imply a positive relation between the overall change in producer surplus and the industry R&D while a negative coefficient along with a positive CAAR implies a negative one. Given the direction of change in CAAR (i.e. whether it is positive or negative), the expected effect of the case on exclusivity, and the coefficient on the case variables in the R&D estimation equation, we can infer the effect of the case on average on the industry. This will essentially help tie together the estimation results in this chapter with the results in chapter two and in noting if a direct relation is observed among changes in exclusivity, CAAR and R&D, or if the anti-commons argument is upheld. This aspect is further discussed below and illustrated diagrammatically by figures 3.3 (a) and (b) showing the different possibilities that firms can encounter.



Increase in exclusivity: CAR negative and R&D decreases
[$G_0 \rightarrow G_1$, $N_0 \rightarrow N_1$]

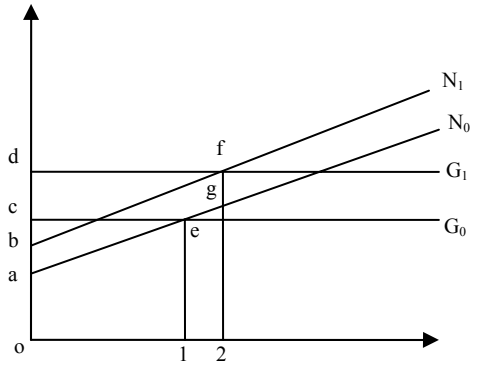
Producer Surplus decreases: triangle (cea) → triangle (dfb)
R&D decreases: quadrilateral (o1ea) → quadrilateral (o2fb)
quadrilateral (21eg) > quadrilateral (agfb)

OR

Decrease in exclusivity: CAR positive and R&D increases
[$G_1 \rightarrow G_0$, $N_1 \rightarrow N_0$]

Producer Surplus increases: triangle (dfb) → triangle (cea)
R&D increases: quadrilateral (o2fb) → quadrilateral (olea)
quadrilateral (agfb) > quadrilateral (2leg)

(i)



Increase in exclusivity: CAR positive and R&D increases
[$G_0 \rightarrow G_1$, $N_0 \rightarrow N_1$]

Producer Surplus increases: triangle (cea) → triangle (dfb)
R&D increases: quadrilateral (o1ea) → quadrilateral (o2fb)
Increase by: quadrilateral (21eg) + quadrilateral (agfb)

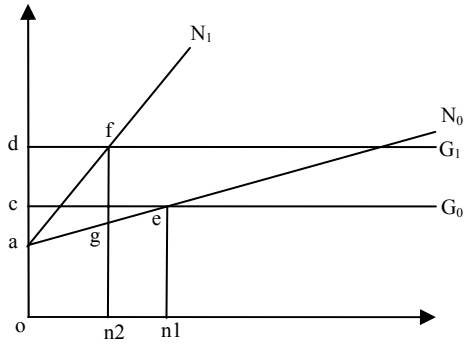
OR

Decrease in exclusivity: CAR negative and R&D decreases
[$G_1 \rightarrow G_0$, $N_1 \rightarrow N_0$]

Producer Surplus decreases: triangle (dfb) → triangle (cea)
R&D decreases: quadrilateral (o2fb) → quadrilateral (olea)
Decrease by: quadrilateral (agfb) + quadrilateral (2leg)

(ii)

Figure 3.3 (a): Diagrammatic illustrations of a positive relation between CAR and R&D



(i)

Increase in exclusivity: CAR positive and R&D decreases
[$G_0 \rightarrow G_1$, $N_0 \rightarrow N_1$]

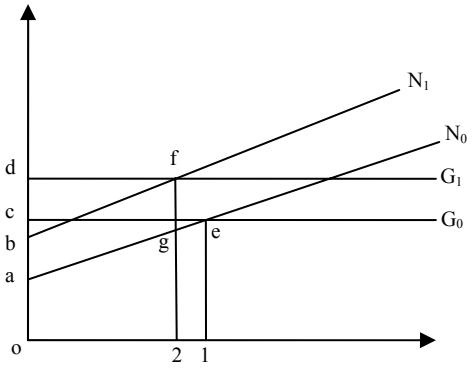
Producer Surplus increases: triangle (cea) → triangle (dfa)
R&D decreases: quadrilateral (on1ea) → quadrilateral (on2fa)
quadrilateral (n2n1eg) > triangle (agf)

OR

Decrease in exclusivity: CAR negative and R&D increases
[$G_1 \rightarrow G_0$, $N_1 \rightarrow N_0$]

Producer Surplus decreases: triangle (dfa) → triangle (cea)
R&D increases: quadrilateral (on2fa) → quadrilateral (onlea)
quadrilateral (n2nleg) > triangle (agf)

Consider eg: a= 1.5, c= 2, d= 3, g=1.7, n2=1.5, n1=2.5;
N_0= 1.5+ 0.3 y, N_1= 1.5+ y



(ii)

Increase in exclusivity: CAR negative and R&D increases
[$G_0 \rightarrow G_1$, $N_0 \rightarrow N_1$]

Producer Surplus decreases: triangle (cea) → triangle (dfb)
R&D increases: quadrilateral (o1ea) → quadrilateral (o2fb)
quadrilateral (21eg) < quadrilateral (agfb)

OR

Decrease in exclusivity: CAR positive and R&D decreases
[$G_1 \rightarrow G_0$, $N1 \rightarrow N_0$]

Producer Surplus increases: triangle (dfb) → triangle (cea)
R&D decreases: quadrilateral (o2fb) → quadrilateral (olea)
quadrilateral (21eg) < quadrilateral (agfb)

Figure 3.3 (b): Diagrammatic illustrations of a negative relation between CAR and R&D

Figure 3.3(a) illustrates circumstances where there exists a positive relation between the CAR of a firm and its expenditure on R&D. In 3.3(a) (i), two cases are presented. First, when there is an increase in exclusivity along with a negative CAR while R&D decreases

and second, when there is a decrease in exclusivity with a positive CAR and an increase in R&D. 3.3(a) (ii) presents a case where there is an increase in exclusivity along with a positive CAR and an increase in R&D, or a decrease in exclusivity with a negative CAR and a decrease in R&D.

Figure 3.3(b) illustrates circumstances where there is a negative relation between CAR and R&D. In 3.3(b) (i), an increase in exclusivity is associated with a positive CAR and a decrease in R&D, or a decrease in exclusivity along with a negative CAR and an increase in R&D. Finally, in figure 3.3(b), (ii), an increase in exclusivity is associated with a negative CAR and an increase in R&D, or a decrease in exclusivity with a positive CAR and a decrease in R&D.

All the above diagrams except 3.3 (b) (i) illustrate circumstances where a positive relation exists between change in producer surplus and the number of inventions 'N'. Figure 3.3 (b) (i) illustrates a situation where this relation does not hold. Here, the change in slope of the N curve from N_0 to N_1 following an increase in exclusivity represents a significant increase in the rate of cost of innovation and the supply of new inventions curve 'N' becoming inelastic. The supply of new inventions curve becoming more inelastic can be explained by the reduction of the availability of input substitutes in production of new inventions as the licensing and transactions costs increase. The gross profit here increases enough for the CAR to be positive in all. The number of inventions 'N' however falls. The increase in the cost of innovation has become discouraging enough to make investment in R&D unattractive although the current gross profits have increased significantly. Compare this with figure 3.3 (a) (i) where the gross profits have not increased as much with an increase in exclusivity. The small increase in gross profits coupled with the increase in the

cost of innovation, causes CAR to be negative in all and 'N' to fall. Increase in the cost of innovation has again been discouraging enough to reduce investment in R&D. In 3.3(a) (ii), gross profits have increased substantially with an increase in exclusivity and though the costs of innovation have also risen, they have not discouraged R&D investment. The CAR here is positive and the number of inventions, 'N' rises. Finally, in figure 3.3 (b) (ii), with an increase in exclusivity the gross profits and the costs of innovation rise. There is a net decrease in producer surplus represented by the negative CAR and the number of new inventions reduces a little. But the increase in the cost of innovation has not made investment unattractive.

Figure 3.3 (a) (ii) and figure 3.3 (b) (ii) represent situations where there is a direct relation between changes in exclusivity and R&D expenses while figures 3.3 (a) (i) and 3.3 (b) (i) represent situations where there in an inverse one. Figures 3.3 (a) (i), 3.3 (b) (i) and 3.3 (b) (ii), all make a case for the anti-commons argument at work where an increase in exclusivity leads to decrease in number of inventions 'N'. This happens because the associated increase in costs of innovation reduces innovations. It can also be noticed here that with an increase in exclusivity either the CAR is negative or the R&D decreases. Only in figure 3.3 (a) (ii) all three of these variables are directly related. In figure 3.3 (a) (i) an increase in exclusivity is associated with a decrease in CAR due to higher costs of innovation and also ends up discouraging R&D. In case of figure 3.3 (b) (i), an increase in exclusivity leads to a positive CAR predominantly due to high gross profits but the increased rate of costs of innovation (as represented by a steeper 'N' curve) has discouraged R&D. Figure 3.3 (b) (ii) shows a more typical case as discussed in chapter two where an increase in exclusivity leads to higher costs of innovation though the rate doesn't change as much. Here,

the higher costs of innovation lead to a negative CAR and a decrease in 'N' though R&D is not discouraged with most gross profits reinvested.

Given these circumstances, if the CAARs (average CARs) were found to be positive from the event study results in chapter two for any selected event in this estimation, then a positive significant coefficient on $(Case\_k)_t$ implies a positive relation between CAAR and R&D, while a negative significant coefficient on $(Case\_k)_t$ implies a negative relation between the CAAR and R&D following the event. Similarly, if the Cumulative Average Abnormal Returns were found to be negative from chapter 2 for any selected event in this estimation, then a negative significant coefficient on $(Case\_k)_t$ implies a positive relation between CAAR and R&D following the event, while a positive significant coefficient on $(Case\_k)_t$ implies a negative relation between CAAR and R&D following the event. Also based on the expected direction of change in exclusivity as discussed in chapter two, an increase or a decrease in exclusivity can be associated with a positive or negative CAAR or a positive or negative R&D case coefficient, to infer whether a direct relation has been exhibited among these variables or the anti-commons argument is upheld.

3.3 Data

Quarterly data on research and development and sales for both pharmaceutical and biotechnology firms are obtained from standard and poor's Compustat files. As already noted in the estimation equation above, the data used is in the form of a quarterly time series and cross sectional data set.

Cumulative average abnormal return (CAAR) values for each of the cases considered in this study, we re obtained using the EVENTUS package and are already presented in the event study analysis discussed in chapter two. Since some of the firms drop out of the

analysis in the event study, they had to be dropped in the current study for the sake of consistency in interpretation. After taking account of these firms, the biotechnology dataset consists of 14 firms while the pharmaceutical industry data set has 11. Further a balanced quarterly data set from 1989- 2005 (68 quarters) is used for the pharmaceutical firms. Because the biotech industry is younger, a balanced data set is available only from 1995-2005 (44 quarters) and that has been used in this analysis. Descriptive statistics on these variables and the list of cases considered for each of the two industries are provided in Table 3.1 below.

Table 3.1: Descriptive statistics and list of cases considered

(a) Pharmaceutical firms

Variable	N	Mean	Standard Deviation	Minimum	Maximum
t	748	34.500	19.64	1.000	68.000
R&D	748	605.397	542.705	0	7123.00
Sales	748	4069.47	2612.03	0	14923.00
Case3	748	0.647	0.478	0	1
Case6a	748	0.529	0.499	0	1
Case6b	748	0.456	0.498	0	1
Case13	748	0.132	0.339	0	1
Case14	748	0.456	0.498	0	1
Case15	748	0.176	0.381	0	1
Case16	748	0.147	0.354	0	1

Notes: 1. Here 't' refers to the number of quarters.

2. The case variables take value 0 till the quarter before the event quarter and then take value 1 for all firms considered in event studies.

(b) Biotechnology firms

Variable	N	Mean	Standard Deviation	Minimum	Maximum
t	616	46.500	12.709	25.000	68.000
R&D	616	61.068	170.664	0	3304.40
Sales	616	187.449	414.221	0	3271.00
Case5a	616	0.477272727	0.499889123	0	1
Case9	616	0.545454545	0.498334254	0	1
Case11	616	0.363636364	0.481436628	0	1
Case12	616	0.204545455	0.403696885	0	1
Case13	616	0.704545455	0.456617598	0	1
Case14	616	0.227272727	0.419410772	0	1
Case16	616	0.363636364	0.481436628	0	1

Table 3.1: Descriptive statistics and list of cases considered (cont.)

List of cases considered (numbered corresponding to table 2.1):

Pharmaceuticals:

Case3- In Re Brana (March 30th 1995)
Case6a- Mova v. Shalala (District Case)(Jan 23rd 1997)
Case6b- Mova v. Shalala (Federal Circuit Case) (April 14th 1998)
Case13- Apotex v. Thompson (Oct 27th 2003)
Case14- Ben venue v. Novartis (June 23rd 1998)
Case15- Warner Lambert Co. v. Apotex Corp (Jan 16th 2003)
Case16- Schering Corp. v. Geneva Pharms Inc (Aug 1st 2003)

Biotechnology:

Case5a- Festo v. SMC (Nov 29th 2000)
Case9- Mylan v. Shalala (Jan 4th 2000)
Case11- Andrx v. Biovail (Jan 17th 2002)
Case12- In Re Buspirone (Feb 14th 2002)
Case13- Apotex v. Thompson (Oct 27th 2003)
Case14- Ben Venue v. Novartis (June 23rd 1998)
Case16- Schering Corp. v. Geneva Pharms Inc (Aug 1st 2003)

3.4 Results

A panel data fixed effects estimation is conducted for both the pharmaceutical firms and the biotechnology firms to take account of the cross sectional heterogeneity using SAS. Table 3.2(A) below reports results for pharmaceutical firms and table 3.2(B) reports results for the biotechnology firms. Tests for heteroscedasticity and autocorrelation were conducted. While biotechnology firms showed no signs of an AR (1) process, the Durbin-Watson statistic shows a significant positive AR (1) process in errors for pharmaceutical firms. Biotechnology firms also did not exhibit significant heteroscedasticity while pharmaceutical firms did. The results for pharmaceuticals are estimated using the parks method[64], which is an option provided by SAS, taking account of AR (1) and heteroscedasticity. Appendix A elaborates on the error structure assumed by this method. Seven different case variables as listed above have been used in estimating R&D for biotechnology and the pharmaceutical firms.

[64] Parks (1967), pg.500-509

Table 3.2 (A): Effect of selected cases on R&D of Pharmaceutical firms: - Parks method estimates using case dummies

Equation Dependent variable- RD							
Intercept SE T value Pr>|t|	59.36519 50.3608 1.18 0.2389	64.90295 47.4742 1.37 0.1720	74.00142 49.0040 1.51 0.1314	71.47985 51.3070 1.39 0.1640	74.00142 49.0040 1.51 0.1314	69.30527 51.8855 1.34 0.1820	71.44838 50.8484 1.41 0.1604
Sales SE T value Pr>|t|	0.123036 0.00541 22.73 <.0001	0.123053 0.00536 22.96 <.0001	0.122865 0.00545 22.54 <.0001	0.123499 0.00540 22.86 <.0001	0.122865 0.00545 22.54 <.0001	0.124243 0.00488 25.47 <.0001	0.122936 0.00561 21.93 <.0001
Trend SE T value Pr>|t|	4.127891 0.6129 6.74 <.0001	3.605538 0.6303 5.72 <.0001	2.680965 0.6317 4.24 <.0001	2.69002 0.4962 5.42 <.0001	2.680965 0.6317 4.24 <.0001	2.538759 0.4747 5.35 <.0001	2.782201 0.5649 4.93 <.0001
CASE 3 SE T value Pr>|t|	-46.9334 19.8983 -2.36 0.0186						
CASE 6a SE T value Pr>|t|		-31.9791 21.0512 -1.52 0.1292					
CASE 6b SE T value Pr>|t|			13.42794 21.1919 0.63 0.5265				
CASE 13 SE T value Pr>|t|				36.05515 20.1489 1.79 0.0740			
CASE 14 SE T value Pr>|t|					13.42794 21.1919 0.63 0.5265		

Table 3.2(A): Effect of selected cases on R&D of Pharmaceutical firms: - Parks method estimates using case dummies (cont.)

CASE 15 SE T value Pr>|t|						47.08903 18.9981 2.48 0.0134	
CASE 16 SE T value Pr>|t|							27.21031 22.1922 1.23 0.2205
R Square	0.7476	0.7356	0.7322	0.7531	0.7322	0.7840	0.7256
Number of Firms	11	11	11	11	11	11	11
Number of Quarters	68	68	68	68	68	68	68
Breusch-Pagan PR>ChiSq	20.21 0.0901	20.07 0.0936	20.29 0.0882	23.41 0.0370	20.29 0.0882	21.39 0.0655	24.19 0.0294
PR>DW	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000	1.0000
PR<DW	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001

NOTE: Pr<DW is the p-value for testing positive autocorrelation, and Pr>DW is the p-value for testing negative autocorrelation.

Time Line

1995				1996				1997				1998				1999			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Case3								Case6a					Case6b Case14						

2000				2001				2002				2003			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
												Case15		Case16	Case13

Table 3.2 (B): Effect of selected cases on R&D of Biotechnology firms: - Fixed effects estimates using case dummies

Equation Dependent variable- RD							
Intercept	12.13492	-3.96981	21.58824	21.58824	-47.1914	-24.9206	-49.1129
SE	39.4434	38.7466	37.8713	37.8713	33.9754	33.7802	34.4878
T value	0.31	-0.10	0.57	0.57	-1.39	-0.74	-1.42
Pr>|t|	0.7585	0.9184	0.5689	0.5689	0.1654	0.4610	0.1549
Sales	0.201754	0.202844	0.196271	0.196271	0.207079	0.201506	0.207132
SE	0.0244	0.0245	0.0244	0.0244	0.0247	0.0246	0.0247
T value	8.28	8.29	8.04	8.04	8.37	8.18	8.37
Pr>|t|	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001	<.0001
Trend	-0.36517	0.087829	-0.56599	-0.56599	1.390448	0.74945	1.446991
SE	0.9028	0.9087	0.8054	0.8054	0.6295	0.7761	0.6520
T value	-0.40	0.10	-0.70	-0.70	2.21	0.97	2.22
Pr>|t|	0.6860	0.9230	0.4825	0.4825	0.0276	0.3346	0.0268
CASE 5a	34.92329						
SE	22.1351						
T value	1.58						
Pr>|t|	0.1152						
CASE 9		21.4515					
SE		22.0886					
T value		0.97					
Pr>|t|		0.3319					
CASE 11			45.61954				
SE			20.8836				
T value			2.18				
Pr>|t|			0.0293				
CASE 12				45.61954			
SE				20.8836			
T value				2.18			
Pr>|t|				0.0293			

Table 3.2(B): Effect of selected cases on R&D of Biotechnology firms: - Fixed effects estimates using case dummies (cont.)

CASE 13 SE T value Pr>|t|					-27.7572 19.4954 -1.42 0.1550		
CASE 14 SE T value Pr>|t|						2.689963 20.0482 0.13 0.8933	
CASE 16 SE T value Pr>|t|							-28.0969 19.5169 -1.44 0.1505
R Square	0.3678	0.3662	0.3702	0.3702	0.3673	0.3652	0.3673
Number of Firms	14	14	14	14	14	14	14
Number of Quarters	44	44	44	44	44	44	44
Breusch-Pagan PR>ChiSq	16.77 0.4008	16.16 0.4421	18.18 0.3136	18.18 0.3136	17.86 0.3324	15.50 0.4880	18.37 0.3027
PR>DW	0.3371	0.3585	0.3395	0.3395	0.3252	0.3751	0.3312
PR<DW	0.6629	0.6415	0.6605	0.6605	0.6748	0.6249	0.6688

Time line

1998				1999				2000				2001				2002				2003			
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Case14								Case9			Case5a					Case11 Case12						Case16	Case13

Tables 3.2 (A) and (B) show the estimation results obtained for pharmaceutical and biotechnology firms. The time line of the occurrence of each of these events is presented at the end of each table. It can be noted that in case of pharmaceuticals, Case 6b- Mova v. Shalala (federal circuit) and Case 14- Ben venue v. Novartis were decided in the same quarter while in case of biotechnology firms, Case 11- Andrx v. Biovail and Case 12- In re Buspirone were decided in the same quarter creating issues of multicollinearity. So the results on these cases are the same and have to be interpreted carefully.

Sales are positively related to R&D and significant for both industries in most cases implying higher investment in R&D by firms with higher revenue. A positive trend in R&D is observed for pharmaceutical firms and also for biotechnology on most instances.

In case of the pharmaceutical firms, Case 3- In re Brana returns a negative coefficient which is significant at the 5% level. Case 13 (Apotex vs. Thompson) and Case 15 (Warner Lambert vs. Apotex) both return positive coefficients which are significant at the 10% and 5% level respectively.

Since the CAARs obtained in case of In re Brana were negative, the negative coefficient on the Case 3 variable indicates that research and development expenses declined significantly following this event. As per the discussion on this case in chapter two, it was noted that the courts had expected the decision to reduce the costs of research for innovative firms as it enabled them to patent their inventions early. Innovative firms were essentially not required to complete the phase two clinical trials on their new drug compounds in order to prove usefulness within the context of patent law. On the other hand, following the anti-commons argument to this decision, early patenting can block off research areas by imposing large costs on innovative firms in similar lines of research. It in effect reduces the research

domain and has the effect of discouraging research. The results here uphold the anti-commons argument. Diagrammatically, this situation is presented in figure 3.3 (a) (i) above.

The positive significant coefficient on the Case 15- (Warner Lambert v. Apotex) variable indicates that research and development expenses increased significantly following the event. This implies that a negative relation exists between the cumulative abnormal returns and the research and development expenses since in this case the CAARs were negative overall. As discussed in chapter two, in this case the court discouraged the practice of 'evergreening' among patent holding firms. It disallowed Warner Lambert from listing its patents directed towards a drug compound which was for an unapproved use. The case was expected to disallow broad listings in the Orange Book. On the other hand, this could reduce regulatory listing expenses and licensing costs for innovative firms. The estimation results here again indicate the possibility of a reduction in regulatory listing expenses and licensing costs encouraging research, as the research and development expenses here increase. Diagrammatically, this situation is presented in figure 3.3 (b) (i) above, and interpreted to reflect a decrease in exlcusivity.

Finally, Case 13- (Apotex vs. Thompson) produces another result where the anti-commons argument seems to hold. For this event, the CAAR was a small negative value for pharmaceutical firms. As discussed in chapter two, this case was decided just a few weeks prior to the passage of the Medicaid Prescription Drug Act in 2003. Here, Apotex contested late listings on the Orange Book made by Smithkline Beechem arguing the need for the FDA to screen late and incorrect patent listings. The Federal Circuit disagreed as the statute did not require the FDA to play the role of screening patent listings. The issue of delisting incorrect listings was discussed once before in Andrx v. Biovail where the court had allowed generic

drug manufacturers to get the FDA listings judicially reviewed. This decision had also faced much dissent since it put the FDA in a situation where it had to make decisions regarding checking the correctness of patent listings though it didn't have the expertise to do so. In Apotex v. Thompson, the Federal Circuit clarified that though judicial review of FDA listings under APA was available to generic manufacturers they would not obtain any benefit from such a challenge. The case in general was expected to have constrained entry from generic drug manufacturers due to the regulatory rules. The CAAR obtained in this case was slightly negative for pharmaceuticals and is coupled with a positive coefficient on the case variable in the estimated R&D equation. Increased exclusivity as discussed before can have the effect of increasing returns but on the other hand, it may have the effect of increasing regulatory listing expenses, increasing licensing costs or transactions costs. The results of this case are best represented by figure 3.3 (b) (ii) above. Here, the increased exclusivity increases the cost of innovation substantially to decrease the producer surplus though the research and development expenses are not discouraged as much. The increases in gross profits are reinvested into research.

Rest of the cases considered returned insignificant coefficients. This may indicate that R&D was not affected from the patent or regulatory amendment. There is a possibility that the dummies are capturing some other noise or incompletely capturing the effect as the regression is over quarterly data. Or, the nature of research and development expenses of adjusting slowly may be causing this observation of insignificant results.

In the case of biotechnology firms, most case variables return insignificant coefficients except for Case 11- Andrx v. Biovail and Case 12- In re Buspirone which return a negative coefficient significant at the 5% level. Case 11 and Case 12 occur in the same

quarter of the same year and hence return identical coefficients and results here. Both these cases were however, expected to have affected exclusivity negatively for patenting firms and the biotechnology firms also returned negative CAARs in both cases. As discussed previously, in Andrx v. Biovail the Federal Circuit allowed generic drug manufacturers to get FDA listings judicially reviewed, putting the FDA in a position to screen the correctness of patent listings associated with approved drugs listed on the Orange Book. While in case of In re Buspirone, anti-trust actions were initiated by a set of generic drug manufacturing firms against BMS because of its multiple late listings. They accused BMS of unlawfully extending its monopoly. The court agreed and also held that the Noerr-Pennington immunity was unavailable to BMS. It explained that the immunity applies in situations where the governmental entity makes a decision based on an independent review of the merits of the petition. The FDA however, acts in a ministerial or non-discretionary fashion in making listings on the Orange Book and so the doctrine was inapplicable. Both these cases together can be best represented by figure 3.3 (b) (i). A decrease in exclusivity here is associated with a negative CAR though the R&D increases. The reduced regulatory, licensing and transactions costs have improved investment in research though the current returns and surpluses have reduced. Here again the anti-commons argument seems to uphold when we consider the effect on the industry as a whole.

The remaining cases considered for the set of biotechnology firms returned insignificant coefficients in R&D estimation. These cases again cannot be interpreted completely in association with the CAARs that were obtained in the previous study.

3.5 Conclusions

In this study, an attempt was made to analyze the effect of marginal changes in exclusivity on R&D of pharmaceutical and biotechnology firms. This was done by relating CAARs obtained from event studies conducted in chapter two using precedent-setting cases, with the research and development activity of these firms following these decisions. Cases that were brought to court since the passage of Hatch-Waxman Act to the introduction of amendments to the Hatch-Waxman Act in the Medicare Prescription Drug Act (2003) were considered.

In summary, three cases returned significant results in case of pharmaceutical firms and two in case of biotechnology. The three cases returning significant results for pharmaceuticals seem to consistently follow the anti-commons argument with either the CAAR or the R&D decreasing with an increase in exclusivity or vice versa. The allowance of broad listing or patenting may lead to substantial increases in the cost of innovation that discourage research or reduce the returns of firms. The two cases which returned significant results in biotechnology were decided in the same quarter of the same year but were expected to have consistently reduced exclusivity. Keeping this in mind, the positive effect on R&D as indicated by the estimation in this study, coupled with a negative CAAR also followed the anti commons argument. It should be noted that these cases which returned significant results spanned over a more recent time frame of 1995 to 2003 approximately ten years since the passage of the Hatch-Waxman Act. The pharmaceutical industry has significantly matured and seems to face the brunt of increased regulatory costs. At the same time, the decision in ‘In re Brana’ indicates that the industry research and development expenses are relatively sensitive to increases in costs of innovation and reductions in research domain. Research and

development expenses of biotechnology firms also seem sensitive to increases in regulatory costs and were enhanced when the courts disallowed broad listings. This supports much of the argument made against allowing a broad scope to biotechnology patents as they can block further inventions from taking place.

While the cases considered here are not necessarily exhaustive in conducting such an analysis they do represent some important cases consistently mentioned in the literature evaluating the patent and regulatory environment since the passage of the Hatch-Waxman Act to the introduction of amendments to the Hatch-Waxman Act in the Medicare Prescription Drug Act (2003).

3.6 Appendix B

Parks Method:

The Parks method is provided as an option in SAS in order to take account of serial and contemporaneous correlation in the errors. In this model a first- order autoregressive model is considered in which the random errors u_{it}, $i = 1, 2 \ldots N$, $t = 1, 2, \ldots, T$, take the structure

$$\begin{aligned}
&\mathrm{E}\left(u_{it}^2\right) = \sigma_{ii} && \left(\text{heteroscedasticity}\right)\\
&\mathrm{E}\left(u_{ij}u_{jt}\right) = \sigma_{ij} && \left(\text{contemporaneous correlation}\right)\\
&u_{it} = \rho_i u_{i,t-1} + \varepsilon_{it} && \left(\text{autoregression}\right)
\end{aligned}$$

where

$$\begin{aligned}
&\mathrm{E}\left(\varepsilon_{it}\right) = 0\\
&\mathrm{E}\left(u_{i,t-1}\varepsilon_{jt}\right) = 0\\
&\mathrm{E}\left(\varepsilon_{it}\varepsilon_{js}\right) = 0 && \left(\mathrm{s} \neq \mathrm{t}\right)\\
&\mathrm{E}\left(u_{i0}\right) = 0\\
&\mathrm{E}\left(u_{i0}u_{j0}\right) = \sigma_{ij} = \phi_{ij}/\left(1-\rho_i\rho_j\right)
\end{aligned}$$

The model assumes heteroscedasticity with first order autocorrelation and contemporaneous correlation between cross sections. For further reference see SAS documentation on TSCSREG procedure, Parks option.

CHAPTER 4

Conclusions and final notes

The main contribution of this study is to an empirical analysis of the effect of changes in exclusivity on the incentives of drug manufacturing firms and research and development expenditure of drug research firms in the pharmaceutical and biotechnology industries since the passage of Hatch-Waxman Act to the Prescription Drug Act amendments. The period of analysis chosen here is relatively recent and less explored. Marginal changes in exclusivity here are evaluated based on decision dates of precedent-setting patenting and regulatory cases which have been documented in the associated literature. Following the changes in the drug approval process that were introduced by the Hatch-Waxman Act, issues regarding listing procedures and entry of generic drug manufacturers arose. These issues were addressed by the courts. Besides regulatory issues some patent issues have also been addressed by the courts. Since both the regulatory environment and the patent environment determine the exclusivity environment that drug manufacturers face, the decisions of courts in these cases were considered representative of the changes to this exclusivity environment faced by drug manufacturing firms. The effect of these changes in the exclusivity environment were analyzed by first selecting a set of relevant precedent-setting cases which are referenced in the literature and then using decision dates of these cases as relevant event dates in an event study analysis on sets of pharmaceutical firms, biotechnology firms and generic drug manufacturing firms. Based on the event study analysis, seven different cases were found to have significantly affected the returns of biotechnology and pharmaceutical firms while generic drug manufacturers did not react very much.

The results from the event study analyses support an inference that the increased regulatory costs imposed on innovative firms like biotechnology and pharmaceutical firms had the effect of reducing their incentives to conduct research. It was noted in this study that cases which led to regulatory changes limiting the range of listings of innovative firms or easing entry of generic drug makers, led to negative returns to patent holding firms. In these circumstances, the revenue lost due to competition from generic drug manufacturers following changes in the regulatory environment may have been greater than any benefits that ensued in the form of reduced regulatory, transactions, licensing or input costs in the research process. With respect to the patenting cases on the other hand, competition among the innovative firms seemed to be of more relevance. The decision in case of In re Brana which was expected to have increased exclusivity returned negative CAARs and Festo (Federal Circuit) which was expected to have decreased exclusivity, returned positive CAARs. Loss of intellectual property domain may have been of more relevance to innovative firms than increased returns due to an increase in exclusivity. In summary, the event study analysis showed that there is some evidence of an increase in regulatory cost imposed on pharmaceutical and biotechnology firms since the passage of Hatch-Waxman and up to the Medicare Prescription drug amendments which caused the returns of these firms to fall. These reductions in returns are also expected to translate into a reduction in research incentives.

The research and development expenditure of pharmaceutical and biotechnology firms was analyzed next to consider its reaction to marginal changes in exclusivity. This was done in a panel setting by regressing research and development expenses of pharmaceutical and biotechnology firms over a period or time, on a set of case dummy variables. Among the

cases considered for pharmaceuticals, In re Brana, returned a negative coefficient which was significant at the 5% level while Warner Lambert v. Apotex and Apotex v. Thompson returned positive coefficients which were significant at the 5% and 10% levels. In the case of biotechnology firms, Andrx v. Biovail and In re Buspirone returned positive coefficients which were significant at the 5% level. All three of the results in case of pharmaceutical firms were supportive of the anti-commons argument laid out in the theoretical model in chapter two. The negative coefficient obtained in case of In re Brana implies a decrease in research and development expenditure following the case quarter. The CAAR obtained on this event was also negative. The decision in the case itself was expected to have allowed early patenting and broadening the scope of patents. While the decision may well have increased the value of any given patent, it appears to impose significant costs of innovation. This result further supports anti-commons concerns. The positive coefficient obtained in case of Warner Lambert v. Apotex implies an increase in research and development expenses following the case quarter. The CAAR obtained on this event was however negative. The decision in this case was seen to have discouraged evergreening among patent holding firms listing their claims on the Orange Book. The result in this case again makes a case for the possibility that the decrease in regulatory listing costs following the decision were sufficient to have encouraged R&D. Finally, the positive coefficient in case of Apotex v. Thompson implies an increase in research and development expenses following the case quarter. The CAAR obtained in this case was a small negative value. This decision essentially affirmed that the FDA played a ministerial role in listing drugs on the Orange Book. However, though the generic drug manufacturers could get FDA listings judicially reviewed, there would be no benefit flowing from the FDA to them from such a review. This was expected to have

allowed patenting firms to continue listing broad claims on their products and stall entry. The small negative CAAR obtained over this decision imply the possibility that pharmaceutical net returns are negatively effect by the sustained regulatory listing and licensing costs which may in turn reduce the number of new inventions produced. The positive coefficient on the case variable following the estimation though imply that the R&D in not discouraged.

For biotechnology firms, though Andrx v. Biovail and In re Buspirone were decided in the same quarter of the same year, they were both expected to have caused a decrease in exclusivity to patenting firms. In case of Andrx v. Biovail, the court allowed generic drug manufacturers to get the FDA listings judicially reviewed which essentially put the FDA in a position to screen these listings. This was not one of its roles as per the statutes. In case of In Re Buspirone, the court held that the Noerr- Pennington immunity is unavailable to patenting firms listing in the Orange Book since the immunity required that the governmental entity in question (the FDA in this case) was required to be making independent reviews of listing petitions. But the FDA in fact only plays a ministerial role and hence the patentee cannot request that the FDA be shielded from efforts influencing legislature regarding trade restraint. The negative CAARs obtained from the event studies in both these cases along with the positive coefficient on the case dummy in the R&D estimation equation, uphold the possibility of decreased costs of innovation such as decreased listing costs and decreased input, licensing or transactions costs, may have been responsible for improved research expenses.

In summary, though not all cases turned out significant for the pharmaceutical and biotechnology firms, the cases discussed above imply that these firms are relatively sensitive to changes in their costs of innovation. In case of pharmaceuticals, relaxation of entry

restrictions may have benefited them to some extent by enabling lower listing and licensing costs or cheaper input substitutes in the innovative process as illustrated by the results in Warner Lambert v. Apotex Corp. On the other hand, an increase in costs of regulation and licensing affected them negatively as illustrated by the results in Apotex v. Thompson. In re Brana also illustrates increased competition among innovative firms over the available patenting domain especially in areas like cancer treatment. In case of the biotechnology firms, increases in exclusivity as expected in Andrx v. Biovail and In re Buspirone affected biotechnology firms negatively upholding the argument that broad patents awarded in the area of biotechnology can be detrimental to research and creating new inventions.

Though the cases considered in this study are not necessarily exhaustive, changes in costs of innovation from changes in the exclusivity environment may have a significant role to play in determining R&D behavior. The event study method in itself provides a useful tool in conducting such an analysis on the effects of regulation since decisions on court cases pertaining to regulation are less likely to leak out and expected to be better captured in comparison with the effect of a change in statute. The insignificant results obtained here in the R&D estimation may however indicate that dummies are capturing other noise or the nature of R&D of adjusting slowing possibly accounts for this observation. Incorporating better data on research that takes into account specific research projects and initiatives that the firms undertake or their licensing behavior may provide some improvement in results.

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