

ESSAYS ON THE U.S. PHARMACEUTICAL INDUSTRY (1984-2013)

by

RUBEN JACOBO-RUBIO

(Under the Direction of John L. Turner)

ABSTRACT

The pharmaceutical industry in the U.S. has changed since the introduction of the 1984 Hatch-Waxman Act. At first look, it seems generic firms are benefiting greatly from the Act, while brand firms are not. In this dissertation, I study the evolution of the industry during the entire life-span of the Act using public, but unique data. In Chapter 1, I study the regulatory background of brand and generic drug approvals. I focus on particular issues to brand firms' attempts at expanding their monopoly protection in light of more generic competition. In Chapter 2, I study the large gap between increasing R&D and flat New Chemical Entity approvals. In particular, I show incremental innovation explains a large part of this gap. In Chapter 3, I study generic firms' challenges on brand patents and the resulting lawsuits that determine generic entry or deterrence. These findings on patent litigation show a large asymmetry between values of entry and deterrence helping explain settlements. My goal with this dissertation is to expand the understanding of the Act's main effects on the U.S. pharmaceutical industry along with its side effects.

INDEX WORDS: Hatch-Waxman Act, Pharmaceutical Performance, Brand Innovation, Generic Entry, Paragraph (iv), Patent Litigation, Settlement, Event Study, First Generic, Incremental Innovation, R&D Productivity, Patents, Exclusivities.

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# Chapter 1

## Background of Pharmaceutical Regulation in the U.S.

### 1.1 The Early Years Before 1984

The history of pharmaceutical regulation in the U.S. follows a pattern of addressing safety and effectiveness concerns, in some cases, after detrimental episodes. For instance, consider the origin of the FDA in 1906. The 1906 Pure Food and Drug Act resulted from a nation-wide battle against unsanitary conditions in the food industry in general. According to the FDA, the 1906 legislation gave it the authority to regulate “interstate commerce in adulterated and misbranded food and drugs,” (FDA History).<sup>1</sup> However, the exact procedure and authority to guarantee drug safety came later on in a series of legislations fuelled by public concerns regarding harmful effects of a couple of drugs.

In 1938 a drug called Elixir Sulfanilamide killed 107 people, including many children (FDA History). This problem arose when the Elixir Sulfanilamide was modified from previous formulations into a poisonous solution with diethylene glycol—a toxic chemical

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<sup>1</sup><http://www.fda.gov/AboutFDA/WhatWeDo/History/default.htm>

similar to antifreeze. The effect of this episode prompted Congress to pass the Federal Food, Drug and Cosmetic Act of 1938. The 1938 law imposed labeling regulations describing safe use for approved drugs; thus, many medications became available only through doctors' prescriptions (Temin 1979, FDA History). Moreover, clinical evidence supporting safety claims became necessary before drugs were approved as part of the New Drug Application (NDA) process for brand-drugs. This law also authorized the FDA to conduct factory inspections to ensure safety.

In 1962, the drug Thalidomide was responsible for another episode of safety concerns due to the birth defects it caused (Harris 1964). The Thalidomide episode led to the 1962 Kefauver-Harris Amendments, giving the FDA authority to require stringent clinical trials to prove drugs are safe and effective. These additional safety and effectiveness requirements permeated even beyond the FDA's realm and into patent regulation. For instance, Engelberg (1999) notes that "after the food and drug laws were amended to require proof of safety and efficacy in 1962, the United States Patent Office took the position that a patent which asserted that a compound had therapeutic utility would not be granted absent proof that the compound was both safe and effective." Although the PTO's position was overturned in court, it planted the seeds for future contentious issues regarding how patents operate in the pharmaceutical industry.

Furthermore, an unintended consequence of the 1962 Amendments was a discouraging environment for generic competition. Prior to 1962, generic firms relied on brand-drugs' safety data to introduce a generic version after brand patents expired. However, the 1962 Amendments created a risk adverse structure and reversed this position by requiring generics to provide the same clinical trials to prove safety and efficacy as brands. This measure duplicated the need for such evidence and created a costly barrier to generic entry. In addition, Engelberg (1999) notes that the 1962 law "contained no provisions for a separate approval process for drugs which were identical to drugs which

had been previously approved.” Instead, there was a vague process for generics under a paper “NDA” process. Therefore, the paper NDA process relied on safety and efficacy data published in medical journals for brand NDAs. However, in practice, not all NDAs with expired patents had published clinical evidence in medical journals. Therefore, a more formal, but still ineffective Abbreviated New Drug Application (ANDA) process had been established after 1962 and before 1984 (see Engelberg 1999 and OB 1980).<sup>2</sup> The uncertainty and lack of effect in the early ANDA process can be appreciated in the more than 150 drugs, with expired patents in the early 1980s, lacking generic entry (Mossinghoff, 1999).

Therefore, in 1981 pharmaceutical regulation took a considerable turn, not so much to do with safety or effectiveness concerns this time, to focus on generic competition. During this period, almost all states favored drug-substitution laws to control health expenditure budgets (Levy 1999). In fact, the first edition of the Orange Book (OB), the official FDA drug approvals list, came as a response from states’ requests to the FDA for a list of therapeutically equivalent drugs that could be substituted for each other (Orange Book 1980). These substitution efforts towards more generic competition created concerns on the part of brand firms for their effective monopoly protection under standard patent law. Standard patent law in general does not require that the invention be profitable, or that guaranteed market protection be awarded to recouperate R&D in specific amounts. Yet, in order to advance this end, Congress worked on patent extensions that would address brand firms’ concerns regarding monopoly protection. According to Engelberg (1999), the 97<sup>th</sup> Congress attempted to address brand firms’ petitions by proposing a seven year extension to patents.

In addition, brand firms also petitioned to keep generic firms from testing brand-drugs’ active ingredients until after patent expiration. This measure would have

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<sup>2</sup>I am not certain at what point between 1962 and 1980 generic applications were officially named ANDAs, but the 1980 OB introduction already uses this term as part of the approval language.

extended effective monopoly for a couple of years past the proposed seven-year extensions due to the FDA's approval process. Prior to 1983, there were mixed court decisions regarding whether testing a drug for a generic application was an act of infringement. Then, in October, 1983, a decision by the District Court of New York, made it clear that generic experimentation was acceptable practice. This decision became known as the Bolar exemption: *Roche Products, Inc. vs. Bolar, Pharmaceutical*, 572 F. Supp. 255 (E.D.N.Y. 1983). Although, the Bolar exemption was reversed by the Federal Court of Appeals, 733 F.2d 858, 221 U.S.P.Q. (BNA) 937 (Fed. Cir. 1984), it later became part of the 1984 Act.

In a second round of negotiations, during the 98<sup>th</sup> Congress, the balance shifted towards encouraging generic entry. Focusing on the increasing concerns regarding cost of pharmaceuticals, Senator Hatch (R-Utah) led the draft of new proposals addressing these concerns. Leading up to the final approval of the Hatch-Waxman regulations, the main challenges were to convince brand firms to accept pro-generic legislation, and to accommodate patent regulation specific to pharmaceuticals. As Engelberg (1999) notes, in brand firms' view, "the combination of: 1) the creation of an expedited generic drug approval process, 2) the Bolar exemption, and 3) the provisions allowing for challenges to the validity of pharmaceutical patents more than offset any possible gain which would be realized from the highly restrictive patent-term extensions." Therefore, to bring brand firms back to the agreement, some changes included going from an 18-month to a 30-month stay for resolution of patent disputes. In addition, patent owners were given the choice as to what patent could be extended under a five-year provision, despite not getting the original seven years brand firms desired. The solution to accommodate patent challenges under patent law was "the creation of an 'artificial' act of patent infringement, which would compel the courts to take jurisdiction," (Engelberg 1999). After these changes were added to the final drafts, the Hatch-Waxman legislation was near ready for final approval.

However, brand firms remained uneasy about some general provisions in the near final draft of the Act. In order to address their immediate concerns, some special short-run provisions were established. Engelberg (1999) notes these exceptions included “a maximum two-year (rather than five-year) patent term extension for promising drug compounds already in clinical trials or under FDA pre-marketing review. [In addition,] a ban on the use of the abbreviated new drug application process for ten years with respect to new drugs which had been first approved between January 1, 1982 and the date of enactment.” The last measure to seal the deal for brand firms was a series of market exclusivities, additional to patents, for several drug innovations, including incremental innovation. Finally, after these concerns were addressed, on September 24, 1984, the Hatch-Waxman bill was officially signed into law by President Reagan as the *Drug Price Competition and Patent Term Restoration Act*, Pub. L. No. 98-417, 98 Stat. 1585(1984).

## **1.2 Regulation Following The Hatch-Waxman Act (1984-2013)**

The 1984 Hatch-Waxman amends the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 and addresses two important problems. On the one hand, it encourages generic firms to enter brand markets. The Act encourages generics via an expedited Abbreviated New Drug Application (ANDA) process which allows generic applicants to avoid expensive clinical trials the reference brand-drug already supports. In addition, there is a special 180-day bounty for the first generic firm to successfully challenge brand patents prior to their expiration.<sup>3</sup> On the other hand, the Act allows brand firms to gain particular market exclusivities (in addition to patents) for their innovations. These exclusivities guarantee a

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<sup>3</sup>Engelberg notes that, “The PMA apparently did not recognize that this provision [180-DE] was a significant incentive to challenge patents and, therefore, it voiced no objection to this provision.” In fact, up until over a decade later in the mid-1990s, this provision did not seem to have much effect (see Chapter 3).

period free from generic competition. The Act also allows for direct extensions to brand patents “for up to 5 years, but the Act also limits the period of post-NDA exclusivity to 14 years,” (Levy 1999, Title II of the Act).

For a brand firm, drug development is long and costly. It begins when a researcher identifies a new molecule. After testing to determine if the molecule is biologically active and to identify what it does (typically in animals), the researcher (often financed by a pharmaceutical manufacturing firm) files an investigational new drug application (IND) to start trials in humans. In these clinical trials, the applicant must prove safety and efficacy.<sup>4</sup> If successful, the applicant files a New Drug Application (NDA) with the FDA; if the FDA approves the NDA, the applicant may sell the drug in the U.S.

Furthermore, the Act requires the FDA to keep a list of “product and method-of-use patents that might be infringed if a generic drug was marketed before the patent expired. This list of patents would be published by the FDA in its list of approved products, i.e. The Orange Book,” 21 U.S.C. 355(b)(1), 355(j)(2)(A)(vi) (1994). Therefore, 1985 is the first full year when patent and exclusivity listings are published.

The distinction between patent protection and FDA exclusivities is important. Exclusivities are granted directly by the FDA and are categorized by clinical importance (i.e., substantial changes to a drug receive more important exclusivities). Therefore, incremental innovation reflected in FDA exclusivities carries a higher cost in most cases. In contrast, patents are granted by the U.S. Patent and Trademark Office (PTO). As a result of this gap from the PTO to the FDA, not all patents represent as significant clinical discoveries as new indications. However, for this reason, patents may be more appropriate indicators of gradual innovation.

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<sup>4</sup>Trials follow a strict, costly three-phase process. See Bradford et al. (2013, section 2.1) for further details.

## 1.2.1 FDA Exclusivity

FDA exclusivities vary from 6 months to 7 years. Most exclusivities incentivize innovative firms to provide clinical evidence on safety and efficacy. However, the Patent Challenge exclusivity (180-Day Exclusivity) incentivizes generic firms instead. Most exclusivities originate with the 1984 Act, except where noted in Table 1.1.

Table 1.1: *Exclusivity Codes*

Name	Abbreviation	Years	Description
New Chemical Entity	NCE	5	For a new ingredient never marketed before; it defines the purest monopoly status.
Orphan Drug	ODE	7	Created under the Orphan Drug Act of 1983, for drugs treating up to 200,000 people or less.
Indication	I	3	Starts with 34 subcategories (1985), now has 681 subcategories (2014).
New Product	NP	3	Starts with one category (1985), now has 2 subcategories (2014).
New Dosage Form	NDF	3	Starts in 1985 and has no subcategories.
New Patient Population	NPP	3	Starts in 2001 and has no subcategories.
Miscellaneous	M	3	Starts with one category in 2000, now has 135 subcategories (2014).
New Dosing Schedule	D	3	Starts with 11 subcategories (1985), now has 138 subcategories (2014).
New Combination	NC	3	Starts in 1985 and has no subcategories.
New Strength	NS	3	Starts in 1985 and has no subcategories.
New Ester or Salt	NE	3	Starts in 1985 and has no subcategories.
New Route	NR	3	Starts in 1985 and has no subcategories.
Rx to Otc Switch	RTO	3	Starts with one category (1985), now has 3 subcategories (2014).
Pediatric Exclusivity	PED	0.5	Created in 1997-FDA Modernization Act, for drugs tested for conditions in infants.
180-Day Exclusivity	PC	0.5	Granted to the first generic firm to successfully challenge brand patent(s); first appears in 1988 Addendum.

**Note:** All the 3-year exclusivities are for additional changes to a label if requirements are met. The 3-year exclusivity application must: (1) “report new clinical investigations (other than bioavailability studies);” (2) that are “essential to approval” of the application; and (3) that are “conducted or sponsored by” the applicant (21 C.F.R. 314.108). The count of subcategories in the 3-year exclusivities is as of May 01, 2014. If noted that exclusivity starts in 1985 is because this is the first year I observe it, but may have been enforced since late 1984.



The NCE exclusivity protects main active ingredients from the very beginning of their life-cycle. In order to obtain the NCE exclusivity, three-stage clinical trials are required, and this makes it the most expensive of all exclusivities. Due to the cost and reward, the NCE exclusivity is the most valuable, but also the hardest to obtain. The NCE exclusivity is the most valuable of all exclusivities because, while it is not the longest, it defines the purest and widest monopoly. For instance, not only is the very first drug protected for five years under this exclusivity, but also all other NDAs containing the NCE are protected from generic competition during this monopoly stage. Figure 1.1 illustrates this concept, where the first stage is the *wide monopoly stage*. However, the farther away additional drugs are introduced from the original NCE approval date, the shorter/narrower their protection.

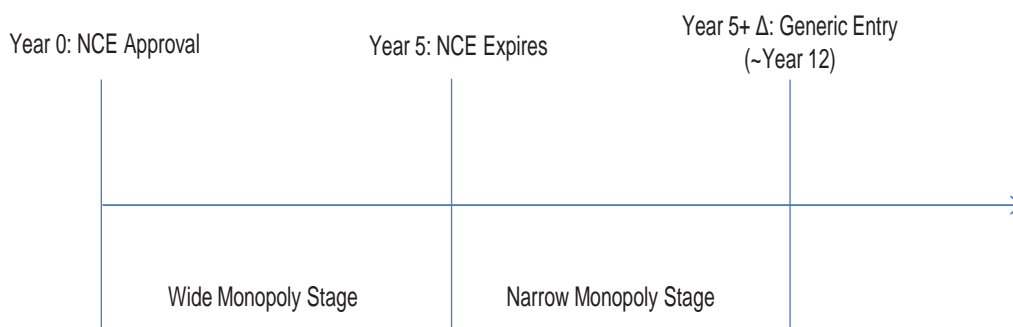


Figure 1.1: *Monopoly Stages*

**Note:** The year of generic entry is an overall average at the ingredient level.

In addition to the NCE exclusivity, other exclusivities protect innovative changes at different stages beyond, or during the five-year period. First, consider the 3-year exclusivities, which protect very specific incremental innovations. These incremental innovations may include new indications, new formulations etc. Moreover, sponsor firms may decide to introduce a completely separate NDA for any of these incremental changes, or they can also peg it to the label of an already approved NDA. For this reason, the 3-year

exclusivity categories require less expensive clinical evidence than for NCEs. This additional clinical evidence is submitted to the FDA via efficacy supplements. Once these supplements are approved, the FDA assigns respective exclusivity codes which are published in the Orange Book.

Furthermore, while it is entirely possible that any additional 3-year exclusivity runs concurrently to the NCE exclusivity, these exclusivities are most valuable if they extend monopoly beyond the five-year NCE protection. However, any potential monopoly extension beyond the five-year mark is very product-specific and does not translate to the entire family of drugs originally protected under the NCE. For this reason, the second stage in Figure 1.1 is defined as the *narrow monopoly stage*. As an example of how product-specific these exclusivities are, consider Prozac and a few other drugs containing the same New Chemical Entity (Fluoxetine Hydrochloride). Although Prozac and Prozac Weekly treat the same condition, the latter has a New Dosage exclusivity while the former does not. Even within Prozac itself, the capsule version is a different product from the tablet version albeit delivering the same dosage. Moreover, Sarafem, a drug containing the same NCE as Prozac, is considered a different product even if its tablet form is exactly the same as Prozac tablet. The reason Sarafem and Prozac have different 3-year exclusivities is because they tread different conditions. These examples illustrate that there could be multiple exclusivities for different versions of drugs containing the same NCE. Therefore, overlapping exclusivities can extend brand monopoly during the narrow monopoly stage, and this happens in almost all cases. Thereby, delaying first entry in the overall market for an active ingredient until about year 11.8 after NCE approval, on average.

In addition to the five-year NCE exclusivity and the prolific 3-year exclusivities, innovator firms can also obtain the Orphan Drug Exclusivity (ODE). In order to obtain the ODE, the respective drug must be the first to treat the orphan condition. The ODE does

not necessarily have to be awarded to the first wave of drugs resulting at the time of NCE approval; it can be awarded to NDAs that follow later on.

The Pediatric Exclusivity differs from other exclusivities because it extends any existing market exclusivity or patent by six months. In addition, the respective drug need not be successful in treating a pediatric condition; it suffices to conduct pediatric testing.

The 180-Day Exclusivity allows the generic challenger to enter earlier than the challenged patents' expiration while also blocking additional generic competitors for 180 days. Under special circumstances this exclusivity is granted to multiple generic firms.

## 1.2.2 Patents

Patents differ from exclusivities in duration and strength. Patents can protect more than one product; thus, they are broader than exclusivities. In addition, patents are granted for 17 years from issue date, up to June 8, 1995; after that date, patents are granted for 20 years from filing date. Moreover, if the application date is before June 8, 1995, the patentee can choose which terms it prefers. The change from 17 to 20 years is part of the TRIPS Agreements.<sup>5</sup> However, even with 20 years of patent life, clinical testing can consume up to half of patents' life-span, for the first wave of patents protecting candidate drugs, before market approval. Furthermore, patents may be challenged by competitors, making their effective protection shorter.

Outside of pharmaceuticals, patents do not generally block entry. Rather, they grant their owners the right to seek damages "after the fact," in court, from firms that infringe. Within the U.S. pharmaceutical industry, however, the regulatory environment carried out by the FDA makes patents a clear deterrent due to the fact that generic applications claim bioequivalence to a referenced brand drug. The FDA monitors safety and efficacy in order to grant approval of brand and generic drugs. Hence, declaring

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<sup>5</sup>Agreement on Trade-Related Aspects of Intellectual Property Rights, Part II, Section Five, Article 33.

bioequivalence makes it easier for a generic to be approved as safety has already been demonstrated by the respective brand drug. However, declaring bioequivalence, also translates into a clear infringement of the brand drug's patent that claims the chemical structure of the active ingredient (i.e., the main patent). In addition to the main patent, a brand drug may also be protected by other patents that claim its use or formulation (i.e., pill, capsule, etc.). Hence, in order for a generic firm to compete in the brand firm's market for a particular drug, either the generic applicant waits for expiration of the patents, or challenges them before they expire. Indeed, FDA regulations lead frequently to scenarios where the outcome of patent litigation determines whether a brand firm maintains a status-quo monopoly or a generic firm is able to enter.

To see how these scenarios emerge, consider the unique design of the Hatch-Waxman Act. The law includes provisions to both stimulate innovation of new drugs and to facilitate entry by generic manufacturers into markets for established drugs. To stimulate innovation, the Act extends patent protection to allow firms to recapture time spent completing clinical trials. To facilitate entry, the Act permits generic manufacturers to bypass clinical trials by filing an Abbreviated New Drug Application (ANDA). An ANDA applicant may rely on safety and efficacy data previously submitted (in connection with an NDA for an approved drug) as long as its drug is bioequivalent to that approved drug. However, the FDA will not approve an ANDA until two hurdles are cleared by the generic applicant. First, all non-patent exclusivity protection needs to have expired. Second, all patent protection needs to have expired as well, or the ANDA applicant needs to prove that its ANDA does not infringe valid patents. For example, consider the monopoly stages in Figure 1.1; in the most common scenario, during the NCE exclusivity period (wide monopoly stage), the brand firm does not even need patent protection because the FDA will not approve any other firm to sell the protected drug. However, once

this exclusivity expires, chemical entities enter a second stage (narrow monopoly stage), monopoly is still the status-quo but other firms may seek to enter.

Therefore, the Act opens a window of opportunity for generic firms during the narrow monopoly stage. For instance, the first Paragraph (iv) generic applicant to successfully obtain approval is awarded a 180-Day Exclusivity (180-DE). A successful entrant must provide in its ANDA to the FDA:<sup>6</sup>

(A) a certification, in the opinion of the applicant and to the best of his [or her] knowledge, with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under Paragraph (i) or subsection (c) of this section,

- (i) that such patent information has not been filed;
- (ii) that such patent has expired;
- (iii) of the date on which such patent will expire, or
- (iv) that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted; and

(B) if with respect to the drug for which investigations described in Paragraph (i)(A) were conducted information was filed under Paragraph (i) or subsection (c) of this section for a method of use patent which does not claim a use for which the applicant is seeking approval under this subsection, a statement that the method of use patent does not claim such a use.

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<sup>6</sup>Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355); Section 505; Subsection (j)(2)(A)(vii)(IV).

Effectively, if a brand firm has valid patents covering components of an approved drug, that the generic must use to make the necessary generic version of the drug showing that it is bioequivalent to the approved drug; then, the FDA will not approve the ANDA.

The four different types of certifications (A)(i)-(iv) are known, respectively as “Paragraph (i)-Paragraph (iv)” certifications. Paragraph (i) or (ii) certification requires merely checking the Orange Book to ensure no patents are in force on the referenced brand drug, while Paragraph (iii) certification requires specifying an entry date that occurs after a patent’s expiry. As long as the generic is not simultaneously seeking Paragraph (iv) certification with respect to another patent, Paragraph (i)-(iii) certifications do not lead to patent litigation and the generic manufacturer typically can enter. When a firm pursues entry under Paragraph (iv), however, the FDA temporarily blocks entry as soon as the brand firm initiates a patent infringement lawsuit in response to the certification.

The FDA Orange Book lists three basic types of patents: compound, formulation and method-of-use.<sup>7</sup> Under Section (B) above, the generic can often satisfy the FDA’s requirement for granting the ANDA, with respect to method-of-use patents, by specifying that it will not sell the drug for the patented methods. This does not prevent the brand firm from suing the generic for patent infringement, but it does mean that the FDA will not base its decision to grant ANDA approval, and entry, upon the outcome of litigation over this patent. In contrast, compounds in pharmaceutical patents are typically claimed by their chemical structure. To receive ANDA approval, a generic must essentially copy this chemical structure in its drug. Hence, compound patents would nearly always be found infringed in Paragraph (iv) patent lawsuits. A generic firm may still win a patent

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<sup>7</sup>See 314.53 of FDA regulations regarding patents allowed to be listed in the Orange Book. For a full discussion of pharmaceutical patents and FDA regulations, see FDA proposed rules on patent listing requirements at 67 Fed. Reg. 65,448-65. In addition, while process patents are not allowed in the OB, product-by-process patents were allowed in the early years following the Act. These patents are problematic because some product-by-process patents are essentially process patents disguised as product patents (FTC 2002).

lawsuit against a compound patent by successfully arguing that it is invalid. For patents covering formulations, however, the generic may win either by showing invalidity or non-infringement.

After submitting the ANDA (iv) letter to the FDA, the generic firm serves notice to the brand firm, typically within 20 days.<sup>8</sup> The brand firm has 45 days, from the date it receives notice of the ANDA (iv) filing, to initiate a lawsuit—subsection (j)(2)(A)(vii)(IV) of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355).

In a Paragraph (iv) lawsuit, the generic firm has to prove that the patent facing a Paragraph (iv) certification is invalid or that it will not be infringed in order to have its ANDA approved. To prove invalidity, the generic firm must show that the patent does not satisfy the statutory requirements of novelty, utility, and non-obviousness. Patents can also be invalidated if the brand firm deceived the Patent Office during the application process (inequitable conduct). To prove non-infringement, a challenger must show that its product's specifications fall outside the scope of the patents' claims.<sup>9</sup>

If successful in court, a generic applicant communicates this information to the FDA. The FDA then approves the ANDA and the generic firm can sell its drug. If the generic firm is unsuccessful in court, the brand firm's monopoly effectively continues. Hence, the fate of attempted generic entry hinges crucially on decisions in Paragraph (iv) patent infringement suits. Because these decisions are made by humans (i.e., jurors and judges), they are random. Moreover, the long-run distribution of victories is symmetric to defeats, 50-50 for either party (Chapter 3).

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<sup>8</sup>No later than 20 days after the date of the postmark; or if the certification is in an amendment at the time at which the applicant submits the amendment.

<sup>9</sup>Patent infringement suits are heard in the Federal District Courts throughout the United States. As they are civil litigations, either party is entitled to request a trial by jury. While jury trials are more common, bench trials occur as well. Once a decision is reached, a written opinion is published in the Federal Register. If a party to litigation appeals the district court decision, the appeal is heard by the Court of Appeals for the Federal Circuit, which has handled appeals of U.S. patent cases since its establishment in 1982.

Brand firms have high incentives to list as many patents as possible, and to sue challengers because even when losing these cases, litigations can extend monopoly due to the duration of the proceedings. Moreover, if brand firms sue within a 45 day window, the FDA's approval of the ANDA is stayed until the earliest of: (1) the patents expire; (2) a court decision is issued; (3) a 30-month stay expires (see FTC 2002).<sup>10</sup> For cases where the FDA approves an ANDA (iv) due to the expiration of the 30-month stay, most generic firms wait until a district court decision to begin marketing. If generic firms launch at risk before a favorable court decision; then, they may be liable for lost profits to the brand firm if they lose the case. In addition, the FTC reports that the FDA usually takes over 25 months to approve an ANDA (iv) even when no litigation occurs.

Patent and exclusivity protection should work as incentives for more innovation by expanding monopoly. Their protection guarantees a monopoly period to recuperate R&D investments. For instance, Kaiser (2002) notes that "the patent extensions afforded by Hatch-Waxman actually extended effective patent life by 2.3 years beyond what they would have been without the law." However, monopoly is not always higher for drugs with more patents and exclusivities. Therefore, the disparity between higher rates of incremental innovation without the additional increase in monopoly motivates arguments to extend the Act's original exclusivity terms. For instance, on August 02, 2013, Representative Jason Chaffetz (R-UT) introduced a bill to expand the 5-year NCE exclusivity to drugs not originally intended for this exclusivity (FDA Law Blog 2013).<sup>11</sup> In support of this argument is the fact that protection for NCEs is only 5 years in the U.S., but it is higher in other countries. In Canada, this protection is 8 years (as of 2006). In Europe, the most generous systems allow 8 years of data exclusivity, plus 2 years of market exclusivity, and 1

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<sup>10</sup>In March 2000, the FDA also issued guidelines for what constitutes a triggering court decision.

<sup>11</sup>Accessed December 2013.



additional year if the candidate drug treats a “significant condition.” Lastly, Japan also offers 8 years for NCEs, but 4-6 years for improvements, and 10 years for Orphan Drugs.<sup>12</sup>

### 1.2.3 Side Effects: Issues with Paragraph (iv) Filings

Three major side effects arise with Paragraph (iv) challenges. The first problem arises when interpreting the requirements necessary to earn the 180-DE. The FDA’s initial interpretation indicates that the generic applicant must complete the ANDA (iv); then, successfully defend the lawsuit by having the challenged patent declared invalid, non-infringed, or unenforceable (Korn et al. 2009). The FDA’s interpretation is known as the *successful defense* requirement. This interpretation is aligned with the logic of the Act to reward the first generic firm, and allow it to recuperate litigation costs. Therefore, if no litigation takes place, no need for the exclusivity.

However, the successful defense requirement interpretation was tested in *Mova vs. Shalala* (1998).<sup>13</sup> In this case, issues arose when a first generic was engaged in a pending litigation while a subsequent filer (not eligible for the 180-DE) was not sued. Furthermore, the second generic’s ANDA had been ready for approval before the resolution of the first generic firm’s case. The first generic argued that the FDA could not approve a second firm’s ANDA until expiration of the 180-DE of the first ANDA (iv); even if this exclusivity had not been officially granted under a clear generic victory yet. The case was resolved in favor of the first generic firm. As a result of the *Mova vs. Shalala* decision, after 1998, a court decision of dismissal, a certified settlement, or a clear district court decision of non infringement/invalidity of patents can trigger approval and enforcement of the 180-Day Exclusivity. Therefore, the 1998 decision strengthened the “property” rights of the first generic applicant under a Paragraph (iv) challenge.

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<sup>12</sup>Comparison of the Non-patent Drug Exclusivities Available in the United States, Canada, Europe and Japan. [www.fasken.com](http://www.fasken.com). Accessed May 2014.

<sup>13</sup>955 F. Supp. 128 (D.D.C. 1997), aff’d, 140 F.3d 1060 (D.C.Cir. 1998).

A second problem with the Paragraph (iv) process pertains to anticompetitive agreements between brand and generic firms. At its best, the 180-DE is only half pro-competitive because competition is truncated to only the first filer(s). At its worst, the unclear triggering of the 180-DE makes it possible to create bottlenecks and delay additional entry. For instance, there is not a clear process that triggers the 180-DE for a generic firm who is awarded the 180-DE but delays marketing. In this setting, the brand firm has an incentive to pay off the generic firm to “park” its exclusivity. This arrangement is accentuated by the fact that brand firms stand to lose about five times as much as the first generic has to gain (see Chapter 3). This large asymmetry of payoffs clearly indicates brand firms have a surplus to pay off the generic competitor and still earn a profit. Due to the anticompetitive effects of the 180-DE, it is no surprise that “parking” of the 180-DE became outlawed after the 2003 MMA amendments (Public Law 108-173).

Paragraph (iv) litigation settlements have evolved and may no longer include direct cash transfers to avoid prosecution. For instance, brand firms may also introduce their own generic versions, so called authorized generics (AG), to compete with their generic challengers (FTC 2011). AGs can be used as settlement tools where brand firms agree to license, discontinue, or not market an AG; in return, generic firms agree to delay their own product launch. According to Levy (1999), the practice of AGs begins in the early 1990s “with Merck’s formation of West Point Pharma, a division established to market generic versions of Merck’s drugs that lost patent protection.” Just as with traditional generics, AGs can bring substantial savings to consumers. However, Aitken et al. (2013), show that average prescription prices may be higher in a “triopoly” scenario (brand, an authorized generic, and a generic competitor) than in the duopoly case (brand and generic) during the 180-DE. Another way in which settlements have evolved is by delaying generic entry to some time before patents expire. These two approaches, avoid direct cash transfers and timing of generic entry, make it harder for the Federal Trade Commission (FTC) to bring

down such settlements. The FTC tracks these settlements since 2005, and it estimates that they are costing consumers \$3.5 billion dollars a year due to delays in generic entry (FTC 2010, FTC 2013).

The legality of settlements has been a contentious issue with many interpretations, and as of June 2013, there is not a single rule that condemns them or allows them altogether. According to the FTC (2010), regarding *Cardizem CD Antitrust Litigation*, 332 F.3d 896 (6th Cir. 2003), “[i]n 2003, an appellate court held that such agreements were automatically (or per se) illegal.” However, other courts do not entirely support the FTC’s position. For instance, in a case relating to the drug AndroGel, the 11<sup>th</sup> Circuit Court of Appeals argues that, “the patent holder ha[s] a ‘lawful right to exclude others’ from the market,” *FTC vs. Watson et al.*, (677 F.3d 1298). Under that interpretation, settlements fall within the scope of those lawful rights. Moreover, the Supreme Court had declined to hear a reverse payment case in 2005, *Schering-Plough vs. FTC*, 402 F.3d 1056 (11th Cir. 2005), but decided the AndroGel case on June 17, 2013, *FTC vs. Actavis et al.*, (570 U. S. 12-416, 2013). The Supreme Court’s decision did not completely eliminate or made the settlements illegal. Instead, in a 5-to-3 decision the Court remanded the case, and essentially instituted a “rule of reason” for courts to apply to such cases. Furthermore, the Supreme Court instructed the 11<sup>th</sup> Circuit Court of Appeals to hear the FTC’s antitrust claims for the AndroGel case in particular, and paved the way for the FTC to make an antitrust argument in other cases.

The third complication is multiple 30-month stays. For instance, multiple generic firms can have first-filer status if they file Paragraph (iv) ANDAs the same date, file with respect to different patents (prior to 2003), or with respect to different versions of the brand drug. This is a complication, not because there may be too many generics firms, but because multiple 180-DE cases also trigger multiple 30-month stays. This loophole gives brand firms the incentives to list as many patents as possible. However, after 2003 multiple

stays for different patents are eliminated. Even without the multiple 30-month stay provision, brand firms have learned to use multiple patents to their advantage, including weak patents. Cooper and Yoshitani (2007) observe that “[o]nce the thirty months have passed, the brand-name companies may withdraw the infringement suit, thereby avoiding judicial review of the patent.”

Furthermore, generic firms can also file for a stay during the lawsuit. This is problematic because a generic firm can file with respect to two patents: one that expires early and one that expires later. The earlier patent may be stronger, but challenging it gives first-filer status to the challenger, even without the intention to actually fight it in court. In this scenario, the first generic firm can stay the proceedings until near the expiration of the first patent and eliminate the 180-DE incentive to truly challenge the first patent by another firm (Herman 2011).

The 2003 Medicare Modernization Act amendments deal with many early issues regarding the 180-DE and the 30-month stay. Therefore, the newer generations of ANDAs after 2003 are referred to as “new ANDAs” (Korn et al. 2009). The bottom line is that with the 1998 and 2003 legislative changes, the 180-DE, 30-month stay, and settlements, are regulated as follows:

- The first generic applicant can block other generic firms even if its Paragraph (iv) litigation case is pending (as of 1998).
- There are not multiple 180-DE periods to different generic firms for challenging different patents, but multiple 180-DE periods remain if different generic firms challenge patents covering different products of the same drug (e.g., different formulations, dosages etc.). Multiple 30-month stays for different patents is also eliminated when the patents relate to the same drug (as of 2003).

- Generic firms forfeit their 180-DE if they do not market within 75 days after it has been triggered (as of 2003).
- As of 2003, under the MMA, “pharmaceutical companies must file certain agreements with the FTC and the Department of Justice within ten days of their execution,” (FTC 2010).

## **Chapter 2**

# **Brand and Generic Performance in the U.S. Pharmaceutical Industry Following the Hatch-Waxman Act (1984-2013)**

### **2.1 Introduction**

The 1984 Hatch-Waxman Act has two goals: encourage generic entry and brand innovative output. However, brand innovation as measured by New Chemical Entity (NCE) approvals, compares poorly to R&D investments, specially after 1996. Brand performance, in terms of NCEs alone, is more alarming after the early 2000s, when for the first time R&D productivity declines under 1 NCE per billion of dollars, compared to 5.1 in 1985. Therefore, this apparent problem with brand firms' performance is not a short-run spurious event. In addition, this seemingly low brand performance coincides with a high rate of generic entry, ranging from 85 annual generic application approvals in 1990 to 516 in 2012.

However, pharmaceutical innovation is higher in reality than NCE counts alone reveal. To help explain innovation beyond NCE approvals, I focus on incremental innovation. The evidence in this chapter shows that incremental innovation increases over 50% at the same time when generic entry, patent challenges, and the R&D-NCE gap expands. Therefore, incremental innovation is a side effect of many incentives combined following the Act. Ignoring incremental innovation can lead to incomplete conclusions about R&D productivity suggesting the Act does not provide enough innovation incentives, and it can mislead policy making. Understanding brand and generic incentives following the Act is important because expenditures on pharmaceuticals is the fastest growing component of health care (Duggan and Morton 2010). For example, expenditures on pharmaceuticals already account for 2.1% of GDP (\$325.8 billion) in 2012, and are expected to increase over the next decade (IMS 2013, National Health Expenditures Accounts 2012).

I explore innovation beyond NCE approvals using public, but unique, data on measures of incremental innovation since 1985. I use patents, exclusivity codes (e.g., new indications), and New Drug Applications (NDAs) as indicators of incremental innovation. I find incremental innovation increases by all these measures, but more so by patents, precisely at the time when the gap between R&D and NCEs becomes wider and generic pressure more eminent.

Patents are the main indicator of incremental innovation I rely on because of their strong correlation with R&D expenditures. For instance, simple correlation coefficients indicate patents and R&D share 80% gross correlation—the strongest and most consistent out of all indicators of incremental innovation. This strong correlation means that patents increase at near the same rate as R&D expenditures. Most of this increase in patents is the result of newer NCEs. For example, NCEs approved from 2001-2008 produce 58.36% more patents than earlier NCEs (1985-1992 or 1993-2000). Moreover, time trends show a strong relation between a six-year rolling average of R&D inflows and contemporaneous annual

patent outflows. As a result of the similarity in the two trends, the ratio of patents to R&D is relatively constant at 7.8 patents per billion of R&D, on average, from 1985 to 2013.

Furthermore, I combine unique patent data with R&D at the firm-level to perform Poisson and Generalized Least Squares (GLS) regressions of patent flows on R&D. These regressions net out the effect of other indicators of incremental innovation, and they robustly confirm that R&D productivity increases over time. For instance, the coefficients on time interactions with R&D show that net R&D productivity is higher after the late 1990s by about one patent per \$US billion increase in a six-year R&D rolling average.

In addition to patents, I use exclusivity codes as a second measure of incremental innovation. Exclusivity code flows exhibit a gross correlation over 60% with R&D. In addition, the most recent cohort of NCEs (2001-2008) shows 66.13% more exclusivity codes than earlier cohorts. However, exclusivity codes come second to patents, regarding gross correlation, because they require additional costs to show clinical merit. For instance, Eisenberg (2005) notes that “trials are not only costly, but also pose a risk of exposing previously unrecognized toxicities, thereby reducing rather than expanding product demand.” As a result there are less exclusivity codes per R&D dollar than patents. For instance, the gross R&D productivity is 5.55 exclusivity codes per \$US billion of R&D.

New Drug Applications (NDAs) also serve as indicators of incremental innovation because a single NCE yields a variety of incremental NDAs. In general, the average R&D productivity is 9.5 NDAs per \$US billion of R&D. Although this R&D productivity is higher than patents or exclusivity codes, its correlation with R&D is insignificant. This low correlation stems from the fact that NDA approvals are relatively flat across time. The flat NDA trend suggest that this type of incremental innovation within NCEs across time is also relatively stable. For example, the 2001-2008 NCE cohort only has an average of 8.11% more NDAs than previous cohorts.



The perfect data to qualify pharmaceutical innovations would measure the actual effect of drugs on consumers' quality/quantity of life. A project of this magnitude, for the entire industry, precludes the use of such perfect data. However, rich measures of incremental innovation all the way from 1985 to 2013 allow to fill several gaps in understanding U.S. pharmaceutical performance during the entire life-span of the Act.

The FDA publishes records for small-molecule drugs in the archive commonly known as the Orange Book (OB).<sup>1</sup> I use OB records for every year during 1985-2013; as a result, I observe NCEs and all their incremental innovation in the form of patents, exclusivity codes, use codes, and NDAs ever listed during the entire life-span of the Hatch-Waxman Act. In addition, the OB also contains standard and patent-challenge generic approvals for these NDAs.

NCEs are a sort of parent drug because they are first time approvals, and subsequent drug approvals are traced to original NCEs. The term NCE is similar to the more general term New Molecular Entity (NME), but NCE strictly applies to small-molecule drugs approved following the Hatch-Waxman Act. For this reason NCEs are the common rubric of innovation performance (Grabowski 2011). However, NCEs differ in many dimensions; thus, simply counting their approvals as the only measure of innovation misses much information (Lanthier et al. 2013).

Incremental innovation is receiving more attention, but patents are excluded from incremental innovation measures despite their strong relationship with R&D. Previous research relies on exclusivities, prescriptions, or changes to drug labels as measures of incremental innovation instead (Berndt et al. 2006; Cockburn 2007). The richness of my data allows me to address shortcomings that causes previous research to ignore patents. Patents are granted by the PTO and not the FDA. This is typically an argument that

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<sup>1</sup>Biologic drug approvals (large-molecule) do not offer the same level of patent detail, and are not subject to the same Hatch-Waxman regulations as small-molecule drugs.

patents do not exactly reflect clinical advances (Engelberg 1999; Bulow 2004; Hemphill and Sampat 2011). However, by avoiding additional clinical cost, patents reflect R&D efforts more continuously (i.e., patents are an intermediate output). In addition, Hatch-Waxman regulations encourage patenting of most incremental innovation and listing of as many patents in the OB. For this reason, I use all annual editions of the OB, and this allows me to account for the continuity of incremental innovation both within drugs and at the industry-level over time. Beyond OB information, I classify patents into those that contain active ingredient claims and those that do not for all patents listed in the OB between 1986 and 2010. I also observe the number of drugs and dollar sales patents protect, and whether they face generic challenges.

I use R&D expenditures for the industry from Compustat. These R&D data include an unbalanced panel of 612 public firms reporting R&D from 1970 to 2012. Moreover, 106 firms match directly to firms in the Orange Book (OB), and this allows me to perform useful firm-level regressions. The firm-level regressions can test for productivity across time, and they also reveal a skewed distribution of productivity in terms of patents. According to these R&D data, the ratio of R&D to revenue increases from 5% to 18% during this period.

The increase of R&D expenditures, and the rise in incremental innovation, serve as evidence of incentives to innovate following the Hatch-Waxman Act despite high generic success. When all incremental innovation per NCE is considered, innovation is not stagnant even if NCE counts are.

### **2.1.1 Related Literature**

This chapter relates to three major areas of research. The first area is the general performance of the industry, both brand and generic firms, following the Hatch-Waxman Act. Generic success following the Act is easy to measure. For example, Levy (1999) reports that generic prescriptions before the Act amount to 18.6% in 1984, compared to

84% in 2012 (IMS 2013). However, brand firms' flat performance by NCE approvals generates mixed reactions. For instance, Morris (2012) studies Hatch-Waxman regulations from 1984-2003, and argues that the period she studies is also a period of "brand-name pharma's drastic change in fortune." In addition, Munos (2009) offers a more empirical setting for the evaluation of innovative performance since the 1950s to 2008. Interestingly, according to Munos, New Molecular Entity approvals have remained relatively flat, even before the 1984 Act. Hence, he concludes that, "contrary to common perception, the new-drug output is not depressed, but may simply reflect the limitations of the current R&D model." Munos questions whether too much credit is given to the Act and argues that its effect on brand innovation may be marginal at best. Engelberg (1999) shares a similar view, and argues the Act contains as many good as bad deals for brand firms; thus, rendering the overall effect on brand firms neutral. Therefore, Engelberg concludes the original provisions of the Act have outlived their presumed usefulness and most of them should be eliminated. In contrast, Missinghoff (1999) asserts the Act is not as bad for brand firms, but also notes that it could improve if brand firms receive more incentives. Notably, Grabowski (2011) offers an overview of the industry going as far back as the early 1960s to the mid-2000s, and offers a positive outlook for future innovation post Hatch-Waxman legislation.

The second branch of literature my work contributes to is incremental innovation in the industry. Cockburn (2007) and Berndt et al. (2006) study ways to expand measures of incremental innovation as determined by new indications and International Classification of Diseases (ICD-9) prescription categories, but they do not use patents. Patents are excluded from measures of productivity in this industry, perhaps as a result of how patents are used to abuse certain regulatory loopholes. For instance, Hemphill and Sampat (2011b) argue the many "weak" patents in the OB contain high noise levels due to their heterogeneity, and it is not clear they represent substantial clinical advances. In addition, Bulow (2004)

points out that patent strategies to game the system renders them questionable. However questionable the use of patents, their strong link to R&D remains uncontested.

The third literature I contribute to is the R&D-patent link more generally. Early work on R&D and patenting shows that patents are a strong indicator of R&D productivity across many industries (Griliches and Pakes 1984; Hall et al. 1986). Griliches and Pakes (1984) propose a reduced-form model with patents as the dependent variable and lagged measures of R&D as explanatory variables, along with some other indicators of innovation as controls. The reason patents are a strong indicator of R&D productivity is that patents account for intermediate results of R&D and for final discoveries. However, Ernst (2001) points out patent data limitations, arguing that “not all inventions are patentable; not all patentable inventions are patented; the economic significance of inventions varies enormously.”

All of these limitations are much less severe in the pharmaceutical industry, as compared to other industries, which makes it an exceptional ground for exploring the R&D-patent link. For instance, Hatch-Waxman regulations incentivize listing of all patents claiming active ingredient, formulation and method of use. In addition, the listing of patents in FDA-public records show exactly how patents vary according to the timing they are listed relative to drugs’ life-cycles, and number drugs they cover. Beyond FDA-records, it is also possible to observe how patents vary in sales they protect, whether a patent is challenged by generic firms, and whether a patent holds up in court.

The data section describes the sources used. The rest of the paper is divided into specific sections addressing each of the major pharmaceutical trends: R&D, NCE approvals, incremental innovation indicators, and generic competition.

## 2.2 Data

Table 2.1: *Data Sources*

	Time Frame	Key Characteristics
<b>Main Sources:</b>		
R&D, Revenue <i>Compustat</i>	1970-2013	Covers all publicly traded companies in North America for the entire pharmaceutical industry.
Drugs, Patents, Exclusivities <i>FDA Orange Book</i>	1984-2013	Comprehensive list of annual listings on drugs (generic and brand), patents and exclusivities.
Priority Status <i>FDA Other</i>	1984-2013	Indicator of approval status.
Drug Sales <i>IMS</i>	1985-2010	Dollar sales and rankings for the top 1000 prescribed drugs in the US.
<b>Additional Sources:</b>		
Paragraph (iv) Lawsuits <i>Derwent Litalert</i>	1984-2010	Covers 50-70% of all U.S. patent lawsuits (most years), includes filing dates, settled cases.
Trial Decisions <i>LexisNexis</i>	1984-2012	Complete opinions include decisions, decision dates, firms, Paragraph (iv) info, patent numbers.
Patent Claims <i>USPTO</i> <i>FDA ANDA Letters</i>	1985-2010	Includes classification of individual patent claims into active ingredient claims and claims without active ingredient reference.

**Note:** R&D from Compustat includes the portion dedicated to biologic drugs. However, a 2013 report by the Pharmaceutical Research and Manufacturers of America (PhRMA 2013) shows the portion of R&D going into biologics for some years.

Table 2.1 lists the data sources I use. The detailed description of each source follows in the Appendix. Pharmaceutical output for small molecule approvals (as opposed to large molecule biological drugs) is recorded in the *Approved Drug Products with Therapeutic Equivalence Evaluations*—Orange Book (OB). The Orange Book is an annual publication dating as far back as 1980; thus, it covers the entire Hatch-Waxman Act life-span. However, outdated editions are discontinued from circulation, hard to obtain, and even

harder to consolidate into a single master file. The difficulty arises because from 1980 (first edition) to the 24<sup>th</sup> edition, the OB is only available in print form. Starting with the 25<sup>th</sup> edition, the FDA publishes PDF and electronic records online.<sup>2</sup> In this chapter, I study every annual edition of the OB from 1985 to 2013, not just the cumulative latest version.<sup>3</sup> The Hatch-Waxman was signed into law on September 24 1984; thus, 1985 is the first complete edition listing patents as part of the these amendments.

There are four general levels of information available in the OB: brand (NDAs) and generic (ANDAs) drug approvals, firms, patent and exclusivity protection. The patent and exclusivity information is contained in the addendum of each edition. Every annual edition of the OB contains previous approvals as well as recent ones. However, recent OB editions omit older information when it becomes obsolete (e.g., patents are delisted, expired or discounted). For this reason, it is important to use all editions when studying long-term trends.

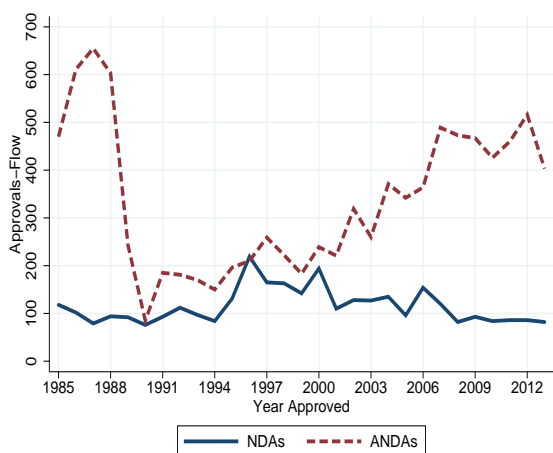
In addition to the OB data, I use patent specific information from ANDA letters and USPTO patent documents to classify patents according to the claims they contain. Other additional data to the OB include data on R&D expenditures from Compustat. I also use data on patent litigations obtained by individually searching drugs, firms and patents for cases (see Chapter 3). Lastly, I merge OB data to annual sales information from IMS during 1985-2010. IMS sales include the top 1000 drugs, and different products of the same drug can be identified in some cases (e.g., Adderall and Adderall XL).

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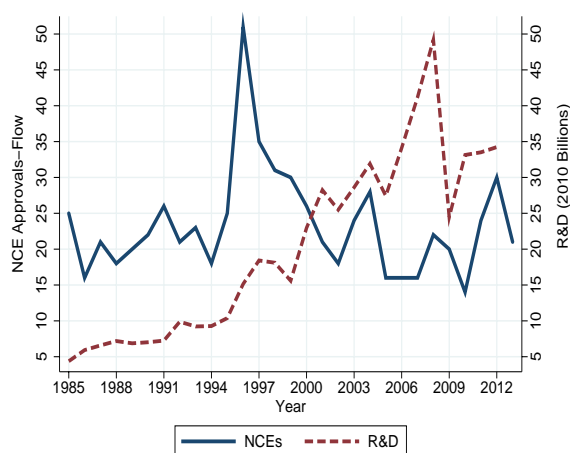
<sup>2</sup><http://www.fda.gov/drugs/informationondrugs/ucm114166.htm>

<sup>3</sup>First, printed editions of the OB were obtained and using OCR software, the data were extracted and then cleaned for consistency.

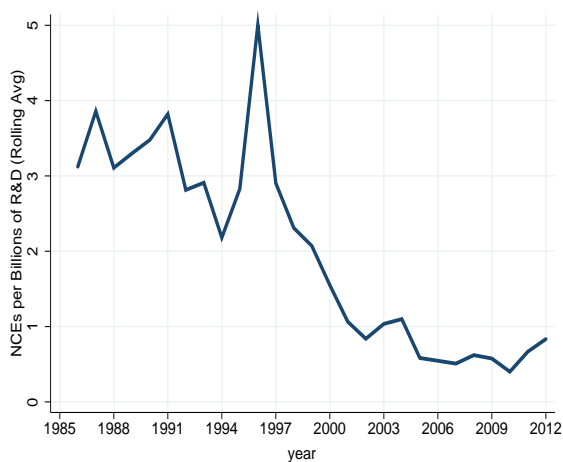
## 2.3 General Performance Trends in the Industry



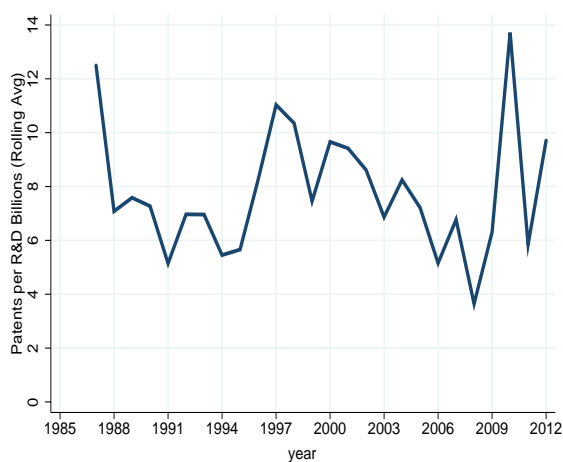
(a) *Generic Approvals vs. Brand Approvals*



(b) *NCE Approvals vs. R&D*



(c) *NCEs to R&D*



(d) *OB-Patents to R&D*

Figure 2.1: *Industry Performance*

**Note:** Figure (a) shows all ANDA approvals even when there are multiple ANDAs per drug. R&D represents a six-year rolling average of all pharmaceutical R&D from Compustat, but excludes R&D dedicated to biologic drugs.

Figure 2.1 shows the industry performance during the entire life-span of the Act, and it provides the motivation for this chapter. Panel (a) compares generic to brand application approvals, and it reveals a widening gap between the two. Panel (b) shows the gap between

NCE approvals and R&D. Both of these gaps occur right at year 2000, begging the question of whether innovator firms innovate in other ways not observed in these figures (e.g., incremental innovation).

Panel (c) shows that the ratio of NCEs to R&D declines over time. Meanwhile, the ratio of patent flows in the OB to R&D, in panel (d), shows that from the late 1990s to the early 2000s is a period of more incremental innovation. These gross comparisons suggest incremental innovation is filling the expanding gap between NCE and R&D. If this is the case; then, other incremental innovation indicators should also increase during this period, particularly for newer cohorts of NCEs.

For a better understanding of incremental innovation within younger NCE cohorts, Table 2.2 shows a breakdown of three NCE cohorts and their respective incremental innovation indicators during their first five years of commercial life. The 2001-2008 cohort is more productive, across all measures of incremental innovation, than the earlier cohorts (1985-1992 and 1993-2000). For instance, the youngest cohort has 58.36% more patents, 66.13% more exclusivity codes, 227.17% more use codes, but only slightly more NDAs than the previous cohort. Moreover, the distinction between priority and standard approval helps understand incremental innovation within these two categories of NCEs. In general, priority NCEs have more patents but less exclusivities than standard NCEs. However, NCEs from the 2001-2008 cohort have almost the same levels of incremental innovation. This is evidence of an increase in incremental innovation across NCEs in spite of, or because of, the decline in NCEs. Therefore, innovation is not necessarily lower in the second half of the Hatch-Waxman; it is just harder to measure by NCE counts alone.



Table 2.2: *Average NCE-Cohort Productivity within First Five Years of Life*

Category	COHORT 1985-1992	COHORT 1993-2000	% Increase	COHORT 2001-2008	% Increase
Patents (All)	2.11 (0.75)	3.53 (1.34)	67.30%	5.59 (1.77)	58.36%
Patents (Priority)	2.23 (0.99)	4.38 (2.33)		5.28 (1.58)	
Patents (Standard)	1.88 (0.48)	2.44 (0.72)		5.80 (2.64)	
Exclusivity Codes (All)	1.50 (1.42)	1.53 (0.49)	2.00%	2.54 (0.79)	66.13%
Exclusivity Codes (Priority)	1.02 (0.78)	1.43 (0.51)		2.59 (1.09)	
Exclusivity Codes (Standard)	1.98 (2.67)	1.67 (0.86)		2.35 (0.58)	
Use Codes (All)	0.73 (0.51)	0.92 (0.21)	26.03%	3.01 (0.80)	227.17%
Use Codes (Priority)	0.77 (0.62)	1.03 (0.36)		2.89 (0.84)	
Use Codes (Standard)	0.60 (0.38)	0.80 (0.23)		3.20 (0.88)	
NDAAs (All)	1.69 (0.24)	1.48 (0.16)	-12.43%	1.60 (0.71)	8.11%
NDAAs (Priority)	1.54 (0.27)	1.44 (0.22)		1.27 (0.31)	
NDAAs (Standard)	1.73 (0.36)	1.52 (0.34)		1.92 (1.99)	

**Note:** (Priority) and (Standard) refers to the NCE cohort, not to the respective category. The cohort years represent when NCEs are approved. Patent output only considers patents in the OB. Percentage increase is relative to the previous cohort. Output information is available through 2013, but the 5 year cut-off constrains the last cohort to 2008.

## 2.4 R&D Investments

R&D is the source of the industry’s existence; without it, no first-in-class innovation occurs, or the incremental innovation that comes after; and to be fair, not even generic competition would exist. Arguably, the high profits that innovator firms earn during their monopolies are to a great extent necessary to sustain their R&D efforts. However, pharmaceutical innovators are not alone in their efforts to pursue new discoveries or improvements to existing ones. The federal government subsidizes part of all R&D in the pharmaceutical industry. According to Kaiser (2002), in 1988, the National Institutes of Health spent “14 cents for every \$1.00 spent by industry on pre-clinical R&D.”

The R&D process includes a lengthy pre-clinical phase where many compounds are first screened, the candidate compounds that make it through are tested in assays and animal models. Then, promising compounds must undergo three stages of clinical trials to establish safety and efficacy in humans. DiMasi et al. (2003) report that, “[i]n phase I, a small number of usually healthy volunteers are tested to establish safe dosages and to gather information on the absorption, distribution, metabolic effects, excretion, and toxicity of the compound.”

The second stage may involve hundreds of patients with the target condition to establish efficacy. The third stage involves thousands of people to establish complete safety and efficacy profiles before market approval (Bradford et al. 2013).<sup>4</sup> Therefore, phase III is the costliest, and there is a large amount of attrition occurring from beginning to end (DiMasi et al. 2003).

In terms of time, Ashburn and Thor (2004) note that the duration of clinical trials, for first-in-class drugs, is 15 years: 7 years in screening and pre-clinical testing, 6 years in clinical trials, and 2 more years on the approval process after successfully completing the

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<sup>4</sup>For more information on the clinical process, see FDA (1999) and DiMasi et al. (1991)

clinical trials. In addition, these phases may overlap and disaggregation of costs during each phase may not be possible (DiMasi et al. 2003).<sup>5</sup>

In terms of dollar costs, Ellery and Hansen (2012) point out that half of these R&D costs corresponds to pre-clinical trials (research, compound screening etc), the other half to clinical trials (development). However, Cohen (2005) notes that since 1976, “the pharmaceutical industry has allocated relatively more funds to clinical research (Phases I to IV) and regulatory functions, at the expense of pre-clinical research.” The monetary cost in pre-clinical and clinical testing is substantial, and it is increasing over time.<sup>6</sup> According to Levy (1999), “real research and development expenditures per new drug approval rose from \$135 million to \$250 million between 1985 and 1995.” These costs increase to \$350 million per NCE in 1990 (Cockburn and Henderson 1996); to between \$625 and \$802 million in 2000 (DiMasi et al. 2003; Adams & Brantner 2006; Light & Warburton 2011); and to \$1.2 billion in 2006 (PhRMA 2013).

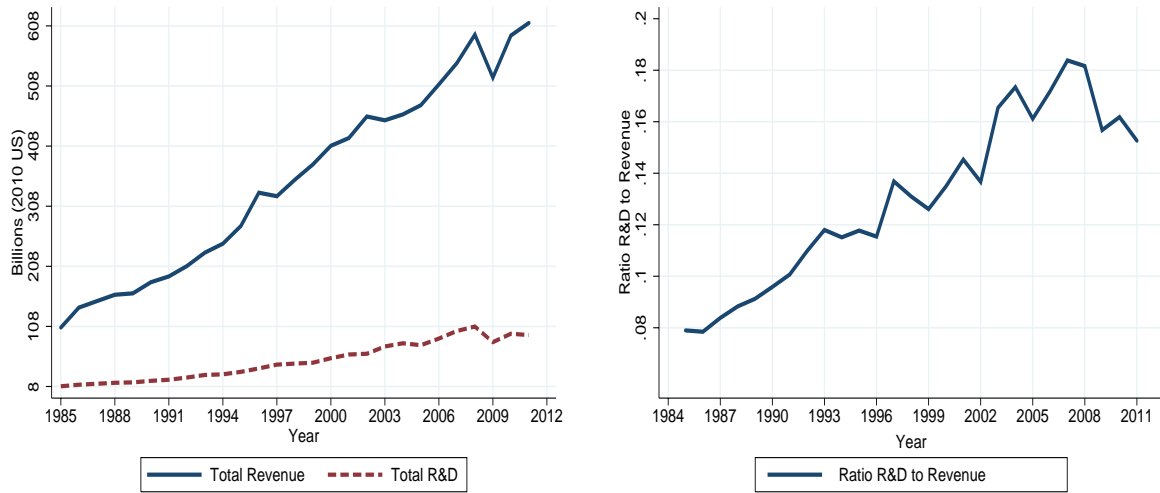
Figure 2.2 represents R&D for a total of 612 pharmaceutical firms from Compustat records.<sup>7</sup> Panel (a) shows annual flows of revenue and R&D in levels of 2010 U.S. \$billions. Panel (b) shows R&D expenditures as a fraction of revenues, and it indicates the industry’s commitment to innovating. For example, starting at 5% of revenue in the early 1980s, R&D rises to about 18% of revenues in the late 2000s. This trend represents a lower bound for R&D expenditures because it only considers public firms. In addition, it excludes social R&D from government or other research institutions (e.g., universities). On the other hand, the R&D expenses reported may extend beyond pharmaceuticals into chemical R&D outside of pharmaceuticals (Scherer 2001).

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<sup>5</sup>Some exceptions to using disaggregated data include Cockburn and Henderson(1996, 167), who study basic research for completely new projects separate from development for incremental innovations on existing drugs. More notably, DiMasi et al. (2003) gather detailed costs throughout the complete pre-approval process.

<sup>6</sup>Cost figures are relative to the year the respective study estimates them.

<sup>7</sup>A trend using only 86 firms (not included) with at least one NCE approval in the OB from 1985 to 2013 follows the same general trend.



(a) *Levels*

(b) *Ratio*

Figure 2.2: *Trends in R&D Investments from 1970-2012.*

**Note:** The sample in these figures includes all public pharmaceutical firms in Compustat (searching by NAICS: 325412). In addition, revenue and R&D are gross annual flows. While it is possible to distinguish R&D net of biologic R&D, this disaggregation is not possible for revenue. For this reasons, both R&D and revenue in this figure include biologic R&D.

Moreover, the average annual R&D expenditures are \$34.71 billion and the average annual revenues are \$259.29 billion (both in 2010 US dollars). Therefore, the general average ratio of R&D to revenues is 13.39% over the entire period. This ratio increases from 7.5% (1980-1990), to 11.8% during (1990-2000), and to 16.12% in the last period (2000-2010). In addition, the grand total of R&D investments, from 1970-2012, sums up to \$1.53 trillion dollars (in 2010 dollars).

The R&D increase, starting in the mid-1980s, is in large part the result of an increase in future expected profits. For instance, Grabowski and Vernon (1996, 269) point out that “price-cost margins rose from 33 percent in the early and mid-1970s to 40 percent in the late 1970s and early 1980s.” This explosion in R&D during the 1980s is also

documented by Cockburn and Henderson (1996). In comparison, the R&D slowdown in the late 2000s could be the result of the most recent U.S. recession, starting in December 2007 and ending in June 2009, rather than a decline in R&D attractiveness.<sup>8</sup>

## 2.5 NCE as a Measure of Innovation

Before discussing incremental innovation, it is important to understand where it comes from. The most direct and common measure of productivity in the pharmaceutical industry is New Chemical Entity (NCE) approvals; or more generally New Molecular Entities (NMEs).<sup>9</sup> In addition, NCE is a term that defines the five-year exclusivity for New Chemical Entities. NCEs are drugs whose main active ingredient is, for the very first time, approved under FDA regulations. Therefore, any incremental innovation in the form of NDAs, exclusivity codes, or patents, is traced back to NCEs.

The evolution of NCE approvals is relatively stable over time. For instance, the average rate of NME approvals from 1963 to 1983 is about 15 a year (DiMasi et al. 2003). Using data from 1985 to 2013, I observe that the number of NCE approvals increases after the 1984 era to 24.5 on average. Despite this increase in NCE approvals after 1984, a common criticism about the industry's output is that NCEs approvals are stagnant around the post 1984 average. More troublesome is the disparity between rising R&D and constant NCE output which often leads to claims that the low-hanging fruit has been picked and that R&D is now focused on harder projects (Moses et al. 2005; Cockburn 2007; Munos 2009; Pammolli et al. 2011). In the media, this phenomenon is called the “drying up” of the pipeline (The Economist 2004; Morris 2012).

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<sup>8</sup>[http://www.bls.gov/spotlight/2012/recession/pdf/recession\\_bls\\_spotlight.pdf](http://www.bls.gov/spotlight/2012/recession/pdf/recession_bls_spotlight.pdf)

<sup>9</sup>NME represents a larger set because it includes NCEs (for small molecule-drugs) and large molecule entities (biologic drugs). The two terms represent completely new drugs, but NCE is a term that became available with the Hatch-Waxman Act.

Figure 2.3 shows all NCEs approved and listed in the Orange Book (OB) from 1985 to 2013. The approval status, priority or standard, is not available in the OB but can be observed from drugs@FDA. This type of breakdown is explained in a three-tier classification by Lanthier et al. (2013).<sup>10</sup> Approval status helps differentiate innovation potential across NCEs according to clinical evidence. The FDA grants priority status to speed up approval of a drug that “demonstrates the potential to provide a significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening condition from a drug that does not demonstrate such a potential.”<sup>11</sup> In addition, the number of priority approvals per year is not limited to FDA approval resources or quota limitations. Priority review is not limited to NCEs and may extend to NDAs in general, or to new indications in particular.

However, review status does not always reflect actual market long-term performance. Moreover, since 2007 a priority review voucher (PRV) can be used to shift priority review to drugs not originally deemed as priority candidates by the FDA.<sup>12</sup> The use of a PRV should still carry some level of innovation information, but how PRVs differ from traditional priority review drugs is not entirely clear.

The remarkable feature in Figure 2.3 is what seems like a major spur in innovation from 1995 to 2000. The annual average number of NCE approvals before and after that time window is 23.4; then, 51 NCEs are approved in 1996, the peak year. Therefore, comparisons of industry output relative to the 1995-2000 ‘golden era’ may lead to conclusions that subsequent approval trends are disappointing. While there is in fact an

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<sup>10</sup>Lanthier et al. 2013 also use BLAs, while I only use NCEs. In addition, when a NCE is approved and then combined with another ingredient, the resulting drug may give the impression that a NCE exclusivity is associated with both the original and the resulting combination. I eliminated 36 cases that may seem as NCEs but are combinations instead.

<sup>11</sup>FDA: MAPP 6020.3 Rev. 2

<sup>12</sup>“The priority review voucher (PRV) is motivated by Ridley et al.(2006) and became law in 2007. Under this law, a developer of a treatment for a neglected disease receives a PRV for priority review from the Food and Drug Administration (FDA) to be used with a product of its choice or sold to another developer.” Accessed January 2014. <https://faculty.fuqua.duke.edu/dbr1/voucher/>

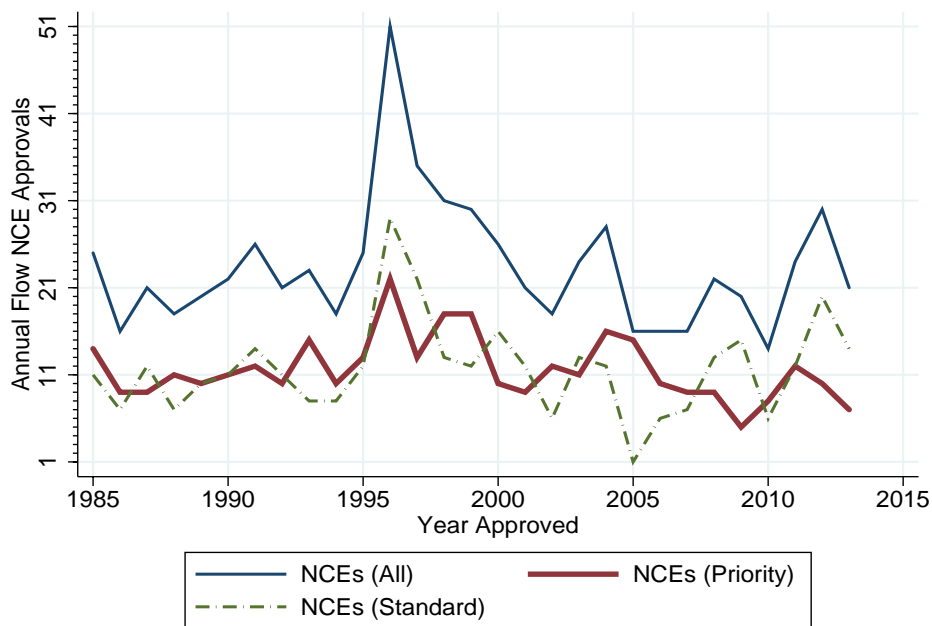


Figure 2.3: *Trends in NCE-Ingredient Approvals by Priority Status (1985-2013).*

**Note:** Sample includes NCE approvals in every annual edition of the Orange Book since 1985 to 2013. It only counts the ingredient observation and not many NDAs introduced the same year for the NCE-ingredient.

increase in NCE approvals during the 1995-2000 periods, two combined effects likely amplify this pattern greatly. First, according to Scott Morton (1999), “[i]n 1989 the generic scandal broke out. Four reviewers at the FDA were found to have been taking bribes in return for speeding approval of ANDAs.” While this scandal relates directly to generic applications; it also delays approvals for brand applications as the review process for any approval became more stringent during that time. Then, in September 1992 a special provision, the Prescription Drug User Fee Act (PDUFA), allows the FDA to charge “fees to the food, drug, and cosmetic industries for any of its regulatory and review activities.”<sup>13</sup> The effect of PDUFA is to speed up approvals in general, and combined with the bottleneck in applications from the 1989 scandal, it makes 1996 an exceptional year in

<sup>13</sup><http://www.fda.gov, history overview>.

NCE approvals. Lanthier et al. (2013) point out that an unprecedented 50% increase in FDA review staff took place as a result of the 1992 PDUFA. Furthermore, the trend of priority and standard NCE approvals very closely match each other, even during the 1995-2000 exceptional period. For instance, the average annual approval rate is 11.66 for priority and 11.72 for standard NCEs. This fact facilitates comparisons to identify other areas in which these two types of NCEs differ.

## 2.6 Brand Side Effects: Incremental Innovation

Incremental innovation is important for a full understanding of the innovative capacity in the industry, especially after 2000, when the gap between NCE and R&D widens.

Incremental innovation accounts for a large portion of this gap, and it is observed from patents, exclusivity codes, NDAs, and use codes. Incremental pharmaceutical output is neglected because of the misconstrued idea that it represents very minor innovations (see Cockburn 2007). However, this is not the case as second generation drugs account for major advances in medicine (CBO 2006).

Table 2.3 shows the correlations between different lags of R&D and all Orange Book innovation indicators. First, the flow of NCEs and NDAs are not significantly correlated with any of the R&D measures. This lack of correlation motivates the idea that R&D is reflected in other innovation indicators. In fact, the correlation between exclusivity codes and R&D is very strong, but less so than patents. Among all indicators, patents have the strongest correlation with R&D. The reason the correlation of R&D is less for exclusivities than for patents, is that exclusivities require additional time and cost in clinical evidence, while patents do not. I now explain some of these indicators of incremental innovation in more detail.



Table 2.3: *Correlations of R&D and OB Performance Measures*

<b>R&amp;D</b>	<b>NCEs</b> (85-13)	<b>NDA<sub>s</sub></b> (85-13)	<b>EXC</b> (85-13)	<b>PATENTS</b> (85-13)
<b>ROLLING AVERAGES</b>				
Rolling Avg 3 yr (0-2)	-0.178 (0.365)	-0.073 (0.696)	0.680* (0.000)	0.779* (0.000)
Rolling Avg 6 yr (0-5)	-0.184 (0.349)	-0.111 (0.554)	0.648* (0.000)	0.813* (0.000)
Rolling Avg 8 yr (0-7)	-0.187 (0.341)	-0.125 (0.502)	0.638* (0.000)	0.817* (0.000)
Rolling Avg 11 yr (0-10)	-0.184 (0.349)	-0.140 (0.453)	0.620* (0.001)	0.826* (0.000)
<b>LAGGED LEVELS</b>				
RD t-0	-0.115 (0.562)	-0.018 (0.925)	0.661* (0.000)	0.703* (0.000)
RD t-1	-0.161 (0.403)	-0.122 (0.506)	0.555* (0.002)	0.678* (0.000)
RD t-3	-0.222 (0.247)	-0.136 (0.459)	0.542* (0.003)	0.787* (0.000)
RD t-5	-0.192 (0.319)	-0.206 (0.259)	0.440* (0.019)	0.810* (0.000)
RD t-7	-0.185 (0.338)	-0.231 (0.204)	0.429* (0.023)	0.815* (0.000)
RD t-10	-0.167 (0.387)	-0.227 (0.212)	0.382* (0.045)	0.820* (0.000)

**Note:** Significance values (\*) at the 10% significance level. Values in parentheses represent significance levels (P-values). R&D extends to the 1970s; thus, allowing the construction of past years averages starting in 1985.

## 2.6.1 Exclusivities

In order to obtain an FDA-granted exclusivity, the sponsor firm must submit clinical evidence to support claims that the drug is safer, more effective, used for a different indication, or target a different population than a established drug version. Therefore, if a drug does not offer substantially any of those added benefits over its original version, no exclusivity is granted. In addition, if a drug is already successful as an off-label prescription, the incentive to get an exclusivity to bring it on-label is lower.

Table 2.4: *Counts of Exclusivity Codes*

<b>Category</b>	<b>1985-2013</b>	<b>%</b>	<b>85-95</b>	<b>96-06</b>	<b>07-13</b>
I-Indication	918	36.87	209	483	226
NP-New Product	302	12.13	32	146	124
NDF-New Dosage Form	257	10.32	103	89	65
ODE-Orphan Drug	228	9.16	68	99	61
PED-Pediatric	180	7.23	na	105	75
M-Miscellaneous	164	6.59	na	54	110
D-New Dosing Schedule	149	5.98	31	80	38
NC-New Combination	141	5.66	49	50	42
NS-New Strength	93	3.73	53	27	13
NE-New Ester or Salt	29	1.16	10	13	6
NR-New Route	16	0.64	10	3	3
RTO-Rx to Otc Switch	6	0.24	3	1	2
W-Waived	4	0.16	0	2	2

**Note:** The two other exclusivities granted by the FDA are PC-Patent Challenge (220 during 1990-2013) and NCE-New Chemical Entity (678 during 1985-2013). Both are excluded from the table.

Table 2.4 shows the count of all the different types of exclusivity codes granted from 1985-2013, and broken down into three different time intervals. These counts relate to all drugs during the 1985-2013 interval, including drugs whose main active ingredient is approved before 1985. Indication exclusivities are the most prevalent; they account for over

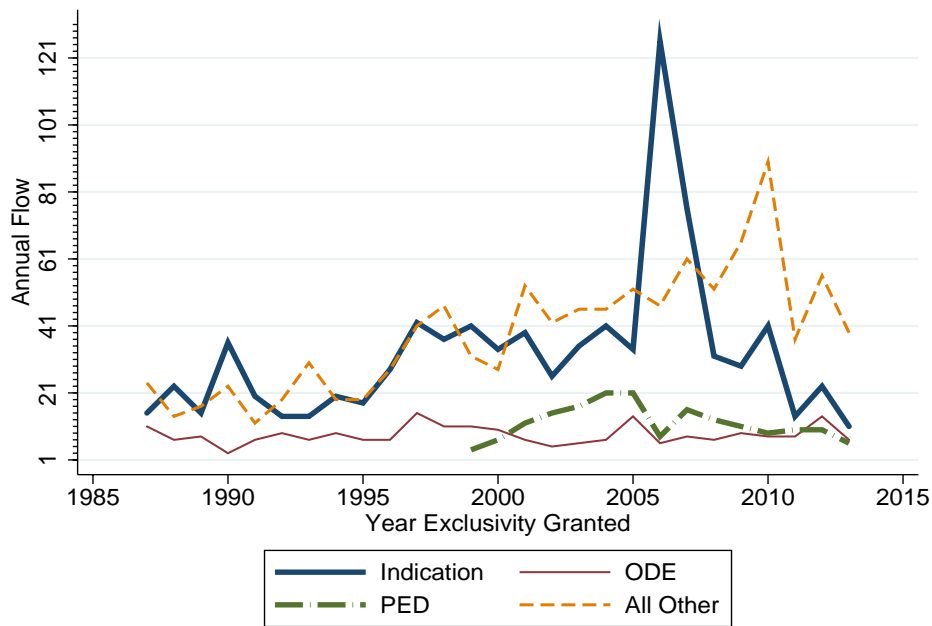


Figure 2.4: *Exclusivity Types*

**Note:** “All Other” represents all the 3-year exclusivity codes except for indication exclusivities.

36% of all exclusivities. Listed in descending order, indication, new product, and new dosage (three-year exclusivities) dominate the landscape. Furthermore, if confined to only drugs that relate to the NCE (1985-2013) cohort, indication exclusivities account for a higher share—over 40% of all exclusivities (not in table).

Figure 2.4, shows the time trends of exclusivity codes (excluding NCE), for the entire window 1985-2013. Indication exclusivities have an average annual flow of 24.4 approvals over the entire period (1985-2013). In addition, the flow of indication exclusivities is higher after 1995 with a clear spike in 2006. In contrast, the flow of Orphan Drug exclusivities remains stable at 5.9 a year. Moreover, the average flow on PED exclusivities is 9.6 per year since 1997, when it first became available. The trend of “All Other” includes all other 3-year exclusivities, except Indication exclusivities; this trend has

an average flow of 18.9 a year. The increase of all the exclusivities codes in general and the introduction of PED suggests that after 1997 drugs enjoy more exclusivity protection than their predecessors.

The timing of additional exclusivity codes is important for extending monopoly beyond the wide monopoly period, after the five-year NCE expires. In general, the average timing of the ODE exclusivity is 2.49 years after NCE approval, and as early as 6.73 years for the PED exclusivity. Furthermore, Ellery and Hansen (2012) note that in current times nearly all drugs have PED, specially because a drug need not be successful in dealing with the pediatric condition it is tested for. Instead, clinical testing alone is sufficient in order to obtain a PED. Indication exclusivities are first introduced, on average, at year 4.48—just before the NCE exclusivity expires. In addition, the cumulative distribution of *all* three-year exclusivities is normally distributed within the period of narrow monopoly, after the five-year expiration and before generic entry.

### **2.6.2 Patents as a Measure of R&D Productivity**

Early work by Griliches and Pakes in the 1980s shows a strong relationship between patents and R&D at the industry-level. At the firm-level, they cannot establish the same strong relationship because of data constraints. I use detailed pharmaceutical data on patents, R&D and other indicators of innovation, and show that with higher quality data, the link between R&D and patents is statistically significant at the firm-level. More importantly, these firm-level regressions confirm that R&D productivity increases over time as measured by patent outflows.

First consider the general specification of firm-level R&D productivity over time, similar to Griliches and Pakes (1984).

$$P_{i,t} = \alpha + \sum_{t=1988}^{2013} I_t R_{i,t} + Z_{i,t} + \eta_i + \epsilon_{i,t}. \quad (2.1)$$

Where  $P_{i,t}$  is the flow of patents listed in the OB under a firm's name (i) in a given year (t). The fact that only OB patents are considered is important because all these patents carry a significant dollar value to innovator firms. This is not typically the case in general; thus, gross patent flows in other industries carry higher noise than in the pharmaceutical industry. Furthermore, the summation term is composed of an indicator variable,  $I_t$ , that takes the value one for the respective year, and zero otherwise. The term  $R_{i,t}$  is the six-year rolling average of R&D as of time (t).<sup>14</sup> For instance, the six-year rolling average as of 2000 includes R&D from 1995-2000, as of 2001 it includes 1996-2001, etc. Moreover, R&D is standardized to 2010 US \$billions. Hence, the combination  $I_t R_{i,t}$  simply considers R&D on a year by year basis, and it represents R&D productivity in a given year compared to a base year (in this case 1987). Furthermore,  $Z_{i,t}$  represents additional controls for innovation (e.g., NCEs, exclusivity codes, NDAs). By including these controls, the coefficients on  $I_t R_{i,t}$  represent net patent productivity. The term  $\epsilon_{i,t}$  represents the variation, or noise, across firms. Lastly,  $\eta_i$  is the variation within firms. Griliches and Pakes (1984, 59) point out that this firm-specific component “reflects differences among firms in their *average* propensity to patent.” In this industry, the propensity to patent is almost certain, at least for active ingredient, formulation, and method of use patents. The implications of a high propensity to patent is that the firm-specific variance,  $\eta_i$ , is much smaller than in other industries, and the econometric assumptions relating to it most likely hold.

One important caveat is that, at the firm-level, R&D includes both small molecule R&D and biologic R&D. This is formally a measurement error, and it makes the

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<sup>14</sup>The reason for a six-year average instead of any other time window is that the gestation lag for patent production is mostly within this interval (see Griliches and Pakes 1984).

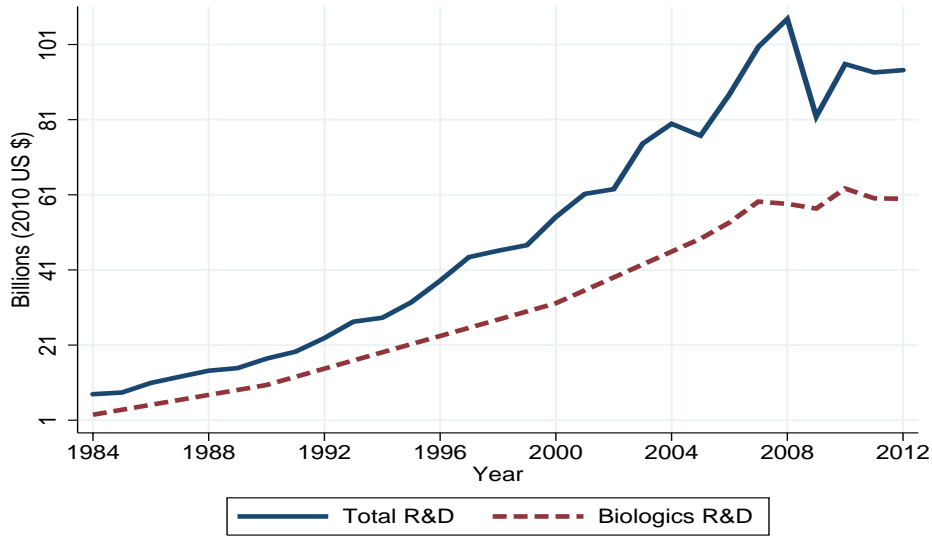


Figure 2.5: *Total R&D and Biologic R&D*

**Note:** Total R&D corresponds to all public pharmaceutical firms in Compustat searching by NAICS:325412, while biologic R&D corresponds to PhRMA reported amounts.

coefficients of R&D productivity, in Equation 2.1, underestimates of the true patent productivity. However, since I am interested in R&D productivity across years and not in a particular firm's productivity, as long as this bias is consistent across years, the underlying analysis holds. This reasoning follows from the fact that this type of analysis is basically a difference in R&D coefficients, all relative to the base year 1987. This is the same reasoning that applies to the firm-specific variance,  $\eta_i$ . For instance, consider the measurement error as the difference between total R&D and biologic R&D:  $e_i = R_i - RB_i$ . If this measurement error is firm-specific and does not vary with time; then, it is simply part of the more general firm-specific variance,  $\eta_i$ . Figure 2.5 shows the relationship between total R&D and biologic R&D at the industry-level over time. This relationship is fairly stable and makes the above assumption plausible at the firm-level. In addition, for this reason, I

perform two regression specifications; one which deals directly with the firm-specific variance ( $\eta_i$ ), and one that remains agnostic about it.

The two model specifications I use to determine R&D-patent productivity are; Generalized Least Squares (GLS) and Poisson, both in a panel setting. GLS directly models the nature and assumptions of firm-effects,  $\eta_i$ . In addition, GLS is a linear regression approach, similar to OLS, but it considers specific characteristics of the variance matrix, including heteroskedasticity and specific correlation in variance components due to different reasons (e.g., firm-effects). The Poisson regression takes on a more general approach via maximum likelihood estimation. Therefore, if the two models yield similar results; then, the GLS assumption, that the within-firm effect ( $\eta_i$ ) is simply noise and does not affect cross-year estimation of R&D coefficients, is a valid one.

**GLS** is the basic approach, and adding the Random Effects (RE) structure of panel data, it follows that:

$$\begin{aligned}
 E(y_{it}|x_{it}, \eta_i) &= x_{it}\beta; \\
 (a) E(\epsilon_{i,t}|x_{it}, \eta_i) &= 0; \\
 (b) E(\eta_i|x_{it}) &= E(\eta_i) = 0; \\
 (c) Rank \quad E(X_i'\Omega^{-1}X_i) &= K; \\
 (d) Var(\eta_i|x_{it}) &= Var(\eta_i).
 \end{aligned}
 \tag{2.2}$$

In the present context, (y) represents patent flows, while (x) represents R&D and other explanatory variables. Equations 2.2 state that the conditional linear estimation is unbiased when assumptions (a)-(d) hold. Assumption (a) is the general strict exogeneity assumption, and (b) is the exogeneity assumption specific to the Random Effects (RE) panel specification. Assumption (c) states the full rank condition, and it means that

equations in the system are linearly independent. For example, there is no double counting of patents for a parent firm and its subsidiary. In addition,  $\Omega$  is the unconditional variance matrix of  $\eta_i$  and  $\epsilon_{i,t}$ . Lastly, assumption (d) states that the conditional variances of the firm-effect are constant, which is not required for consistency, but does yield efficiency.

The RE specification imposes more assumptions than alternative specifications such as Fixed Effects; but in this industry, these assumptions are pertinent and likely to hold. This additional structure makes RE preferable over Fixed Effects because the firm effect,  $\eta_i$ , is treated as a random variable instead of a parameter to be estimated. Hence, under the above specification, the RE coefficients are:

$$\widehat{\beta}_{RE} = \left( \sum_i X_i' \Omega^{-1} X_i \right)^{-1} \left( \sum_i X_i' \Omega^{-1} y_i \right) \quad (2.3)$$

**Poisson** panel specifications directly consider the non-negative nature of patent counts, but do not directly model firm-effects ( $\eta_i$ ). Furthermore, Poisson is typically preferred to other models, such as Negative Binomial or Binomial, because of its simple assumptions. For instance, as Woolridge (2002, 646) points out, “[t]he density of  $y$  given  $x$  is completely determined by the conditional mean  $\mu(x) \equiv E(y|x)$ ”

$$f(y|x) = \frac{\exp[-\mu(x)][\mu(x)]^y}{y!}, \quad y = 0, 1, \dots \quad (2.4)$$

The main assumption in Poisson models is the variance assumption:  
 $Var(y|x) = \sigma^2 E(y|x)$ .<sup>15</sup> The Poisson model is estimated using maximum likelihood methods. Therefore, regression coefficients ( $\beta$ ) are given by (see Woolridge 2002, 648):

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<sup>15</sup>For simplicity, I omit the firm and time subscripts in the present equations.



$$\begin{aligned}
l(\beta) &= yx\beta - \exp(x\beta); \\
\frac{\partial E(y|x)}{\partial x_j} &= \exp(x\beta)\beta_j; \\
\beta_j &= \frac{\partial E(y|x)}{\partial x_j} \frac{1}{E(y|x)} = \frac{\partial \log[E(y|x)]}{\partial x_j}.
\end{aligned} \tag{2.5}$$

Table 2.5 shows the results of the GLS and Poisson panel regressions at the firm-level. I use a six-year R&D average, instead of individual R&D lags, in both specifications to deal with collinearity issues among the R&D lags. In addition, I interact the R&D average with year dummy variables. Therefore, the coefficients of these interactions,  $I.R_i$ , tell how productive the six-year rolling average is in the respective year. In this table, the coefficients of the Poisson regression are incidence ratios (IRR). Therefore, all IRR coefficients are relative to one, and they compare to GLS results which are relative to zero. For instance, Poisson coefficients less than one represent a negative relationship. Furthermore, the coefficients on NCE flows help explain R&D productivity from the firm-level regressions. This is important, because R&D and NCEs are not correlated, but NCEs and patents are.

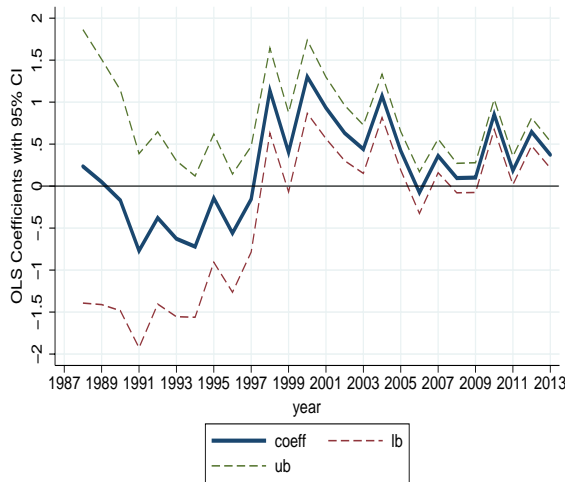
I also run two additional firm-level regressions according to whether patents contain active ingredient claims (not included in table). The results indicate that the productivity of patents covering active ingredient (AI) claims is relatively flat until 2003; then, there is a decline afterward. In contrast, the regression on patents without AI claims indicates these patents are responsible for most of the R&D productivity after 1996 relative to prior years.

More importantly, the regression coefficients in Figure 2.6 show the productivity of R&D in terms of patent flows over time. By both specifications, R&D productivity is clearly higher after 1997 relative to previous years by a difference of about one patent per billion of R&D. These coefficients of productivity are relative to year 1987. Therefore, a

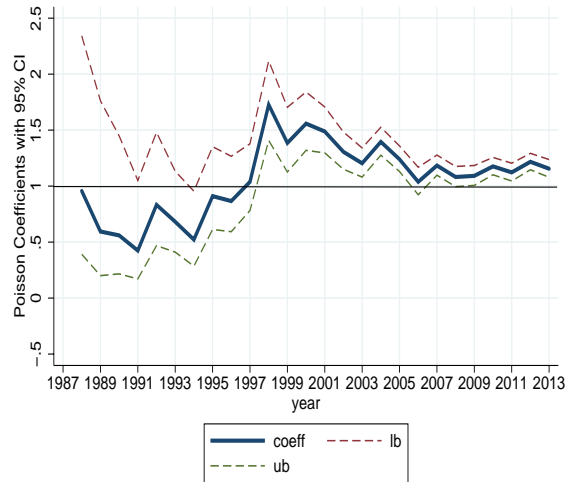
Table 2.5: *R&D Productivity by Patents—Firm Level Regressions*

Variable (Patent Flow)	GLS		POISSON IRR	
	Coefficients	Std Errors	Coefficients	Std Errors
$I.R_i$ 1988	0.235	(0.831)	0.957	(0.437)
$I.R_i$ 1989	0.049	(0.745)	0.595	(0.330)
$I.R_i$ 1990	-0.169	(0.670)	0.56	(0.272)
$I.R_i$ 1991	-0.769	(0.590)	0.424*	(0.196)
$I.R_i$ 1992	-0.379	(0.523)	0.833	(0.244)
$I.R_i$ 1993	-0.627	(0.474)	0.682	(0.177)
$I.R_i$ 1994	-0.721*	(0.429)	0.522**	(0.161)
$I.R_i$ 1995	-0.143	(0.389)	0.91	(0.184)
$I.R_i$ 1996	-0.56	(0.359)	0.867	(0.168)
$I.R_i$ 1997	-0.155	(0.321)	1.038	(0.150)
$I.R_i$ 1998	1.138***	(0.258)	1.727***	(0.180)
$I.R_i$ 1999	0.403*	(0.241)	1.385***	(0.146)
$I.R_i$ 2000	1.302***	(0.222)	1.558***	(0.132)
$I.R_i$ 2001	0.932***	(0.187)	1.488***	(0.104)
$I.R_i$ 2002	0.632***	(0.168)	1.306***	(0.085)
$I.R_i$ 2003	0.440***	(0.147)	1.204***	(0.066)
$I.R_i$ 2004	1.075***	(0.132)	1.395***	(0.064)
$I.R_i$ 2005	0.421***	(0.117)	1.239***	(0.058)
$I.R_i$ 2006	-0.078	(0.127)	1.038	(0.063)
$I.R_i$ 2007	0.360***	(0.102)	1.184***	(0.046)
$I.R_i$ 2008	0.096	(0.090)	1.082*	(0.046)
$I.R_i$ 2009	0.102	(0.090)	1.092**	(0.045)
$I.R_i$ 2010	0.854***	(0.092)	1.176***	(0.040)
$I.R_i$ 2011	0.186**	(0.086)	1.123***	(0.041)
$I.R_i$ 2012	0.647***	(0.085)	1.217***	(0.037)
$I.R_i$ 2013	0.373***	(0.081)	1.155***	(0.040)
NDA's	0.195***	(0.069)	0.992	(0.027)
Indications	0.167**	(0.073)	1.042	(0.026)
NCE's	1.485***	(0.101)	1.583***	(0.055)
Other Exc	0.268***	(0.074)	1.024	(0.028)
Cons	0.232***	(0.057)	0.555***	(0.078)
Alpha cons			1.466**	(0.259)
N-Obs	1,340		1,340	
N-Groups	96		96	
R-sq: within	0.320			
R-sq: between	0.751			
R-sq: overall	0.495			

**Note:** The first variables denote interactions between the six-year R&D average and the respective year (taking 1987 as the base year).



(a) *GLS Coefficients*



(b) *Poisson Coefficients*

Figure 2.6: *Regression Coefficients Over Time*

**Note:** The base line for Poisson Incidence Ratios (IRR) is (1), and it compares to a value of zero in the GLS coefficients. Coefficients for both regressions use 1987 as the base year.

negative number does not mean negative productivity, it just means lower productivity than the base year. This robust result is similar to what time trends show in previous sections. Moreover, the GLS and Poisson yield very similar results, and this means that the assumptions about firm-effects,  $\eta_i$ , hold up.

Furthermore, Table 2.6 shows industry-level regressions. These regressions are much simpler than firm-level regressions because they do not need to deal with firm-level effects. Therefore, simple OLS suffices for the base model, and the Poisson specification is the same as above. At the industry-level, I can net out biologic R&D, not possible at the firm-level. In addition, industry-level statistics do not require exact matching between who lists patents in the OB and who does R&D. Therefore, industry-level data do not suffer from missing values as all the input-output is accounted for. The drawback is that there are less observations to use at the industry-level because each observation is just a year. This

Table 2.6: *R&D Productivity by Patents—Industry Level Regressions*

Variable (Patent Flow)		OLS	POISSON IRR	
R&D Avg		3.162*		1.021***
		(1.621)		(0.002)
R&D Lag0	-5.242**		0.969***	
	(2.247)		(0.003)	
R&D Lag1	-1.473		1.013***	
	(2.460)		(0.003)	
R&D Lag2	5.754**		1.015***	
	(2.153)		(0.003)	
R&D Lag3	-0.337		1.004	
	(2.054)		(0.003)	
R&D Lag4	13.796***		1.082***	
	(4.510)		(0.007)	
R&D Lag5	-10.848*		0.933***	
	(5.320)		(0.007)	
NCEs	1.433	3.361	1.014***	1.032***
	(2.234)	(2.661)	(0.004)	(0.003)
EXC	1.508***	1.510***	1.011***	1.011***
	(0.379)	(0.497)	(0.001)	(0.001)
NDAs	-0.184	(0.785)	0.000	0.995***
	(0.478)	(0.556)	(0.001)	(0.001)
Cons	-29.416	-31.389	26.168***	28.385***
	(45.147)	(60.620)	(2.565)	(2.692)
N-Obs	27	27	27	27
R-sq	0.854	0.646	0.761	0.643
Predicted Pats per \$Billion	7.55	7.80	8.06	7.94

**Note:** At the industry-level, I cannot use a time dummy due to a smaller sample size. “R&D Avg” represents a six-year rolling average. Significance values (\*) at the 10% significance level. “Predicted Pats” indicates the median predicted patents per one billion increase in the six-year rolling R&D average.

drawback prevents the use of interactions between R&D and year variables. In addition, the predicted median productivity ranges between 7.5-8.06 patents. This is in fact the patent to R&D ratios I observe.

## Patents and Drug Sales Trends

After looking at the direct link between R&D and patents, in this subsection I explore sales as an additional factor to help explain the increase in patent activity after 1995. Figure 2.7(a) shows the sum of all patents listed in the OB at any given year, even if approved in prior years. This figure shows the two general patent categories in the OB: patents with active ingredient claims (w/ AI) and patents without active ingredient claims (w/o AI). The latter category includes formulation and method of use patents. The trend of patents w/ AI is consistent with the relatively flat trend in NCE approvals. In contrast, the trend of patents w/o AI is more consistent with an increase in incremental innovation.

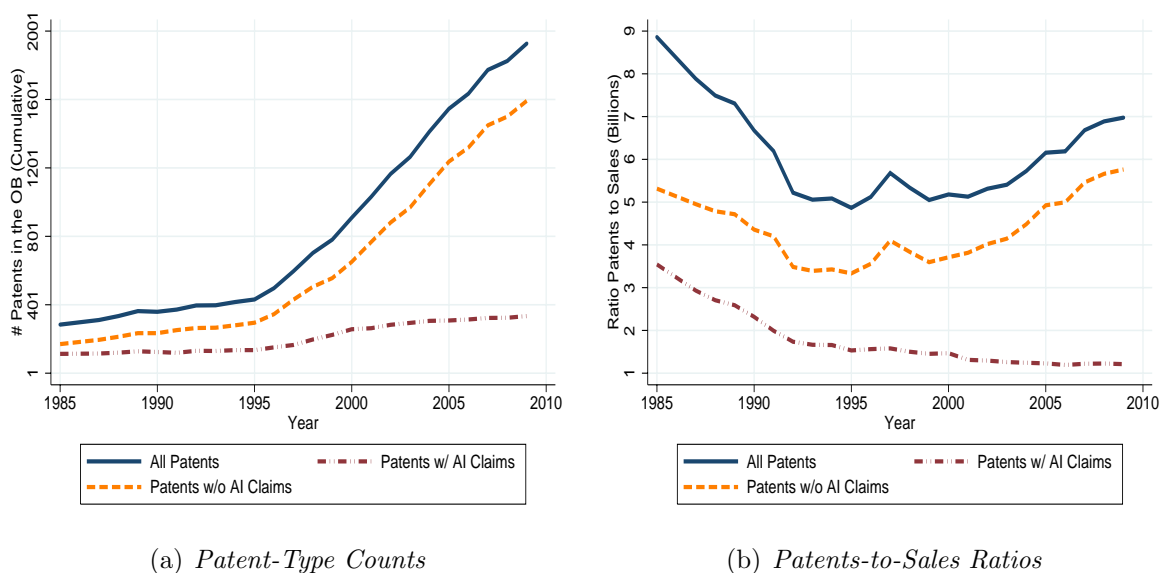


Figure 2.7: *Patent Trends*

**Note:** This figure shows the cumulative count of patents listed in a given year in the OB. The panel on the right shows the same count of patents divided by the annual sales (in 2010 US \$billions) for the top 1000 IMS-recorded drugs the same year.

The increase of patents w/o AI since 1995 coincides with a remarkable increase in sales around the same time. While there is not a single factor that accounts for the increase in sales, some factors that may have contributed to this increase include an expansion in

private insurance plans in the early 1990s. Then, in 2003, Medicare Part-D reforms brought a similar expansion for drug coverage in social programs. In addition, some evidence points to the heavy use in mood stabilizers in nursing homes in the 1990s and early 2000s (Briesacher et al. 2005; Alexander et al. 2011). These types of costs are reflected in Medicare and Medicaid beneficiaries, and these programs represent “almost 60 percent of all prescriptions” (Duggan and Scott Morton 2010). Other factors that account for higher sales include early 1990s horizontal mergers between pharmaceutical firms and Pharmacy Benefit Management organizations (Levy 1999, table II.9). These strategic mergers are important for expanding drug sales because managed care organizations already accounted for a majority of all drug prescriptions by 1994 (Levy 1999, 27). Hence, all these factors overtime help explain some of the increase in sales through an overall increase in demand.

Figure 2.7(b) shows patent-to-sales ratios, and it describes annual cumulative patents listed in the OB divided by total sales for the top 1000 drugs, the same year (in 2010 US \$billions). Therefore, these ratios represent gross patent protection per billion of dollar in sales. Starting around 1995, there are clearly more patents w/o AI claims per billion of dollars. Hence, there is more patent protection for these drugs. However, more patent protection does not necessarily mean longer monopoly periods. The reason is that during the narrow monopoly period these patents can be challenged and defeated. In contrast, patents w/ AI are stronger when challenged, and sometimes not even challenged for that reason. However, Figure 2.7(b) indicates the ratio of these patents to sales declines consistently since 1985.

Furthermore, the acquisition of, and protection by, secondary patents is becoming increasingly more difficult. For instance, in 2007 the PTO issued tougher guidelines for patents to clear the non-obviousness bar. These guidelines make it harder to obtain patents w/o AI. The PTO’s actions are a response to the U.S. Supreme Court’s decision regarding

*KSR vs. Teleflex*, 550 U.S. 398 (2007). This case questions the criteria to prove that an invention is non-obvious (Ellery and Hansen 2012, 94-96).

## 2.7 Generic Entry

The increase in generic competition since the 1984 Act is much more aggressive, compared to earlier years, thanks to the Abbreviated New Drug Application (ANDA) process.

ANDAs originate prior the 1984 Act, but with the Hatch-Waxman Act, a new form of ANDA is introduced—Paragraph (iv) ANDA. In order to achieve early entry, generic firms challenge brand-patents listed in the Orange Book via Paragraph (iv) filings and win the resulting litigation, or brand firms need not respond to the challenge and let generic firms enter.<sup>16</sup> Before the Hatch-Waxman Act, it is estimated that more than 150 products existed without any patent protection and without any generic entry (Mossinghoff, 1999).

Generic entry after patent expiration is also more aggressive following the Act because the generic sponsor need only show that its product is bioequivalent to a referenced drug; thus, avoiding duplication of clinical trials. In fact, generic entry is much encouraged following the Act that even if a referenced brand drug is discontinued, an already approved generic version can serve as the reference drug for other generics. Another way in which regulations help encourage generic approvals is through the recent Generic Drug User Fee Amendments (GDUFA) of 2012. The GDUFA is designed to work as its counterpart, for brand firms (PDUFA-1992), by charging user fees to supplement the cost of the review process and speed up approval.

Evidence that generic companies are benefiting greatly from Hatch-Waxman regulations is easy to show. For instance, generic firms are on average half the time successful when they challenge brand patents in court. This is in large part due to the

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<sup>16</sup>If a brand-patent is not listed in the OB, or listed in a late fashion, a generic firm is not responsible for filing a Paragraph (iv) certification with respect to that patent.

evolution of generic competitors over time. Engelberg (1999) notes that, “[d]uring the 1980s, many of the smaller generic manufacturers were relatively unsophisticated and simply accepted the patent expiration dates listed in the Orange Book at face value.” This is clearly no longer the case.

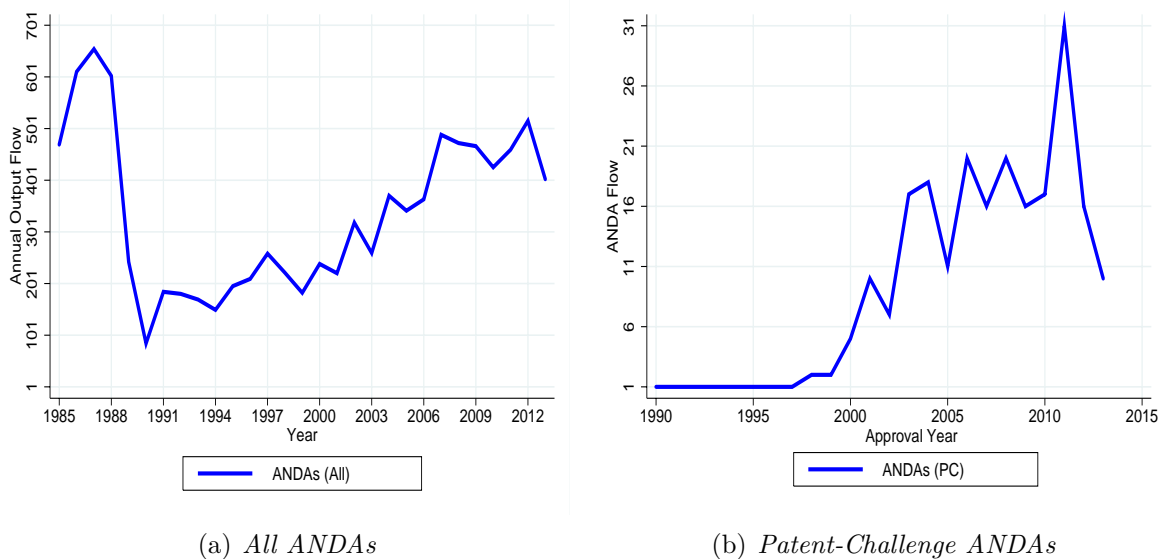


Figure 2.8: *Generic ANDA Approvals*

**Note:** This figure shows all ANDA approvals even when there are multiple ANDAs per drug. ANDA counts are from each annual edition of the Orange Book; thus, they include ANDAs that may have been discontinued.

Figure 2.8(a) shows the progression of generic entry over time as measured by the flow of ANDA approvals from the Orange Book. The first large wave of ANDAs, between 1985 and 1990, corresponds to drugs approved before 1985; ingredients first approved in 1985 can only experience entry no earlier than five years from their approval due to their NCE status. Moreover, from 1990 to 2013 there are a total of 7,191 ANDAs approved. These ANDAs correspond to 677 ingredients. Hence, there are over ten ANDAs per ingredient during this period. In terms of annual flows, the ANDAs approved during this period average a flow of 332 a year. While these high rates of generic competition may seem alarming if generic entry is viewed as a sort of tax on brand innovation, a large tax,



Grabowski and Vernon (1996, 204) point out that generic entry is not as dangerous as direct price regulation.

Figure 2.8(b) shows ANDA approvals as a result of successful Paragraph (iv) challenges. Notably, there are not many of these approvals before the late 1990s.<sup>17</sup> In addition, the increase of ANDA (iv) approvals in 2010 coincides with the sharp increase in patents around the same year and motivates further exploration into these types of patents.

Generic success is appealing to society because of the large savings attributed to generic competition. For instance, savings from generic use in 2012 reach over \$217 billion, and from 2003 to 2012, generics save the U.S. \$1.3 trillion (GPhA 2013). However, Caves et al. (1991) note that, “cost reductions in drugs brought about by generic entry are not being passed along to the consumer, but are instead being captured by other segments of the system, including pharmacies.” On a more careful note, Branstetter et al. (2012) point out that the closer the high rate of generic prescriptions gets to 100%, the closer society is to “starving the golden goose.” For instance, as of 2012, 84% of all prescriptions are already generics (IMS 2013). These observations raise some questions about how much higher generics’ market share can climb before killing the brands’ incentives to be the “golden goose.” For example, according to a *New York Times* article on March 18, 2013, “IMS estimates that use of generics may reach 86 or 87 percent, but will probably not go higher than that.”<sup>18</sup> On the other hand, the high success by some generic firms, such as Teva, has turned them into the golden goose as they introduce their own brand drugs.

However, generic entry and erosion of blockbuster revenues can have consequences in research efforts of rival brand firms. For instance, revenues in pharmaceuticals are highly skewed (DiMasi et al. 2003), and the survival of highly profitable drugs is important to

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<sup>17</sup>In the early years, these type of approvals, though they occurred, may not have been as closely recorded as in recent years. In the hard copies of the OB, 1998 is the first year “PC” exclusivity appears. After that year, OB records start listing more “PC” approvals including those that occurred before the respective year-edition.

<sup>18</sup>“U.S. Drug Costs Dropped in 2012, but Rises Loom,” by Katie Thomas.

keep R&D flowing in. Consider Branstetter et al. (2012) observation that a “10% increase in generic penetration decreases early-stage innovations in the same market by 7.3%.” Supporting the same argument, the Congressional Budget Office (CBO 1998) observes that more generic competition lowers “the average returns from marketing a new drug by roughly 12 percent.” Therefore, while generic success has benefited many consumers, a more careful study into the effects of generic entry on brand incentives is necessary to understand the dynamic effect of competition in this industry.

## 2.8 Conclusion

In this chapter I describe brand and generic firms’ performance following the 1984 Act. I show that the Act has successfully accomplished its generic goal. However, some side effects of the Act include a large number of Paragraph (iv) cases, specially after 1995. The duration and cost of Paragraph (iv) lawsuits can make entry more costly than intended, and generate an increasing number of settlements. The Act’s goal regarding brand firms’ performance is harder to quantify. For instance, New Chemical Entity (NCE) approvals during 1985-2013 is relatively flat over the entire period. However, the NCE flow average is higher by almost ten NCEs post-1984 (24.5) compared to the pre-1984 era (15).

In addition, this chapter shows that the gap between R&D expenditures and NCE approvals is largely explained by incremental innovation. The strongest measure of incremental innovation is annual patent flows. Regressions at the firm-level show that net R&D productivity is higher after the late 1990s. Furthermore, a careful look at NCE cohorts’ productivity reveals an increase in patent productivity per NCE after 2000. These results show that pharmaceutical innovation is higher than measured by NCE counts alone. Therefore, the seemingly decline of innovative output in the second half of the

Hatch-Waxman (2000-2013) is rather a reflection of the difficulty to measure innovation in this industry.

The implication of these findings for further research is a careful exploration into whether the increase in incremental innovation is on net beneficial to society at the aggregate level. On the cost side, the task is easier to accomplish by measuring the additional monopoly profits that result from extending protection beyond original expiration deadlines. On the benefit side, measuring the value of incremental innovation is much harder because it involves many different ways in which consumers benefit from additional indications, improved drugs etc. Yet, at the very least, this cost-benefit analysis of incremental innovation can be done for some therapies if not for the entire industry.

Moreover, my findings motivate further research into the exact timing of incremental innovation relative to generic entry. Exploring this aspect of life-cycle management will shed light on whether generic pressure is increasing incremental innovation output from brand firms. For instance, during the narrow monopoly period, brand firms have large incentives to introduce valuable incremental innovations because of the additional monopoly extension beyond the five-year NCE. Studying this dynamic can help understand if the 3-year exclusivity reward is optimal, or whether there is merit in increasing this exclusivity in some cases. The combination of these additional research projects and the current findings can help future policy making, not only in small molecule markets, but also in biologic regulation.

## Chapter 3

The Private Value of Entry and  
Deterrence in the U.S.

Pharmaceutical Industry (with John  
L. Turner and Jonathan W.  
Williams)\*

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\*Jacobó-Rubio, Turner and Williams. To be submitted to *American Economic Review*.

## ABSTRACT

We study pharmaceutical patent litigation decisions from 1984 to 2012. These decisions are valuable, to brand and generic firms, because they determine generic entry for the first time, or deterrence of such until patents expire. Using an event study approach, and unique data on district courts' decisions, we estimate that brand firms value deterrence of generic entry at \$3.9 billion on average (2010 U.S. dollars). In contrast, the potential first generic entrants value the right to enter, on average, at \$758.7 million dollars. Hence, the value of entry as a percentage of the value of deterrence is 19.4% on average. These estimates account for an appellate process and are robust to alternative sample construction and event windows. The large asymmetry in values sheds light on the incentives these firms have to negotiate settlements instead of litigating.

INDEX WORDS: Hatch-Waxman Act, Paragraph (iv), Generic Entry, Deterrence, Patent Litigation, Settlement, Event Study, First Generic.

## 3.1 Introduction

Generic manufacturing of pharmaceuticals has evolved substantially in the last 30 years. Generics were very uncommon in the U.S. prior to 1984, when congress passed the Hatch-Waxman Act to increase entry. This Act lowers the cost of generic entry and grants a 180-Day Exclusivity to the first generic to successfully challenge a brand manufacturer's patents via so-called Paragraph (iv) Abbreviated New Drug Application challenges. As a result, generic entry has been very successful following the Act. For instance, IMS Health data show that the generic dispensing ratio (percentage of generic to total prescriptions) reached 50 percent in 1999 and 78 percent in 2010, compared to 19% in 1984 (IMS 2011, CBO 1998). Moreover, expenditures on prescriptions in the U.S. reached \$307.4 billion or 2.2% of GDP in 2010 (IMS 2011). Savings from generic use, the same year, were over \$158

billion. Furthermore, in the last decade, from 2002 to 2011, generics have saved the U.S. \$1.07 trillion (GPhA 2012). According to the National Health Expenditures Accounts, health care expending amounted to \$2.6 trillion in 2010 (17.4% of GDP). Rising costs in health care motivate research to answer if and how legislation should encourage more generic entry.

We use an event study of Paragraph (iv) patent litigation decisions to estimate the average private value a generic manufacturer earns by obtaining the rights to be the first entrant in a brand-drug's market, and the average private value a brand firm earns by deterring such generic entry. In typical Paragraph (iv) cases, there is a status-quo brand-firm monopoly and the outcome of patent litigation determines whether the generic is permitted to enter. The discrete effect of exogenous litigation outcomes, on firms' stock-market values, permits us to identify the stakes in the case.

We match litigation decisions, captured from LexisNexis and Derwent LitAlert, to firms' stock-market returns from CRSP. We then use event study regressions to identify, for all litigation events, the cumulative abnormal return (CAR) due to the district court decision. We then aggregate events into four categories of cases: brand wins, brand losses, generic wins and generic losses. For each category, we estimate the average dollar change in firm value. Subtracting the change in value under losses from the change in value under wins yields the stake for an average firm in the district court decision. Applying an adjustment multiple to account for the possibility of reversal on appeal, we arrive at estimates for the average value of entry (using estimates of what generics win and lose) and deterrence (using estimates of what brands win and lose).

Our main results indicate that brand firms value deterring entry, on average, at between \$3.9 billion and \$5.3 billion. In contrast, generic firms value the right to enter at between \$758.7 million dollars and \$781.2 million (all values in 2010 dollars). Hence, the

value of entry is at between 14.6% and 19.4% of the value of deterrence. This suggests that the potential of generic entry significantly erodes total industry profits.

Textbook industrial-organization models of imperfect competition predict that entry by a second producer may significantly reduce (Cournot 1838) or even eliminate (Bertrand 1883) an incumbent monopolist's profit, and that the degree of product differentiation strongly affects the extent of the reduction (Hotelling 1929). In pharmaceutical markets, Frank and Salkever (1997) identify large drops in incumbent sales upon generic entry. Consistent with these other studies, our results suggest that consumers view brand and generic alternatives as goods with a relatively small amount of product differentiation. However, none of these studies directly estimates the value of entry or deterrence, because they cannot account for payoffs under the counterfactual scenario of continued incumbent monopoly.

Generally, the lack of exogenous reasons for the end of status-quo monopolies makes it difficult to directly and precisely estimate the value of entry and deterrence, limiting empirical research on the topic. Of the work that has been done on the topic, much of it has been structural (e.g., Gedge et al. 2013), requiring difficult-to-test parametric and behavioral assumptions.<sup>1</sup> However, in some industries, like pharmaceuticals, features of the regulatory environment generate plausibly exogenous variation to identify the value of entry and deterrence. For example, Snider and Williams (2013) exploit the pro-competitive regulatory reforms introduced by the Aviation Investment and Reform Act for the Twenty-First Century (AIR-21) to quantify the value of eliminating barriers to entry in the airline industry.<sup>2</sup>

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<sup>1</sup>Gedge et al. (2013) develop a dynamic equilibrium model with asymmetric information to capture limit pricing in the airline industry, directly measuring the value of entry and deterrence.

<sup>2</sup>Specifically, Snider and Williams (2013) exploit a sharp discontinuity in coverage by AIR-21, i.e., only airports with two-firm concentration ratios above 50% are covered, and a regression-discontinuity approach to generate exogenous variation in market structure.

The large difference between the average value of deterrence for brand firms and the average value of entry for generic firms also represents the potential bargaining surplus under a settlement of litigation that precludes generic entry for the life of the patents. According to our estimates, settling an average case would yield between \$3.2-4.6 billion of bargaining surplus. Because the generic earns nothing from production under a settlement, but earns a positive expected payoff under litigation, such settlements typically involve a “reverse” payment from the brand to the generic. Shapiro (2003) and Bulow (2004) show that in certain situations a reverse payment alone is sufficient to prove an antitrust violation, and the Federal Trade Commission (FTC) opposes them based on antitrust law. The FTC also argues that such settlements in the pharmaceutical industry cost consumers \$3.5 billion annually in higher drug prices.

The courts have yet to clearly delineate the antitrust implications of reverse payments. Having declined to hear *Schering-Plough vs. FTC* (402 F.3d 1056) 2005, the Supreme Court took on *FTC vs. Actavis et al.*, over reverse payments in a settlement over the drug AndroGel. In a 5-to-3 decision, on June 17, 2013 (570 U. S. 12-416, 2013), the Supreme Court remanded the case, and essentially instituted a “rule of reason” for courts to apply to such cases.<sup>3</sup> They instructed the 11<sup>th</sup> Circuit Court of Appeals to hear the FTC’s antitrust claims for the AndroGel case in particular, and paved the way for the FTC to make an antitrust argument in other cases.

Our study relies on a near-comprehensive set of decisions in Paragraph (iv) patent lawsuits during 1984-2012. First, we compile a historic archive of 3,219 patents, from the U.S. Food and Drug Administration (FDA) “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book) during 1985-2010.<sup>4</sup> Secondly, we search for

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<sup>3</sup>The ramifications of the Supreme Court’s decision extends beyond the pharmaceutical industry because of the challenge to limit the kind of agreements that reduce competition in general but fall within the scope of the patent, see *United States vs. General Electric Company et al.* 272 U.S. 476 (1926).

<sup>4</sup>The key information actually comes from the Patent and Exclusivity Addendum.



details of Paragraph (iv) litigations using LexisNexis Academic and Derwent Litalert. We ultimately identify 159 cases resulting in a Paragraph (iv) decision on patent infringement and/or validity. After removing cases without a status-quo monopoly for manufacture of the active ingredient and cases without a publicly-traded firm, we are left with 93 decisions in our Basic sample. Based upon this sample, we estimate the value of entry at \$758.7 million and the value of deterrence at \$3.9 billion.

In a closely related study, Panattoni (2011) analyzes an event study of 37 brand-firm Paragraph (iv) litigation events during 1984-2007. She uses slightly different sample selection criteria. Most notably, she does not restrict attention to drugs where there is a status-quo monopoly in production of the active ingredient. She also uses the announcement of the outcome of litigation as the basis for the event, rather than the decision date. She does not include generic events, does not estimate the value of entry and deterrence, and does not adjust for possible appellate reversals.

To benchmark our work more closely, we study a second sub-sample of the 159 Paragraph (iv) decisions that meet the Panattoni (2011) selection criteria. Specifically, we use all of her 37 brand events for 1984-2007, and add 45 brand events for 2008-12 for a total of 82 decisions. We then add in generic events that also meet these criteria. Re-estimating the model with this alternative sample (which we call the Announcement sample), we find an average value of entry of \$781.2 million and an average value of deterrence of \$5.3 billion. The primary difference between the estimated values of deterrence is mainly due to the multiple cases in one sample and not in the other.

## **3.2 Data**

The centerpiece of our study is a comprehensive collection of data on Paragraph (iv) patent litigation decisions from the beginning of the modern pharmaceutical industry (1984) to

2012. We first describe how we use multiple data sources to build a comprehensive set of decisions involving Paragraph (iv) cases. In describing this process, we also provide high-level descriptives on trends in patenting and litigation. Next, we describe two different ways to construct samples, from this comprehensive set of decisions, that are appropriate for event study analysis, and provide descriptive statistics for each. Table 3.1 lists all the data sources we use.

Table 3.1: *Pharmaceutical Patent Litigation Data Sources*

	Time Frame	Key Characteristics
<b>Main Sources:</b>		
Drug Patents <i>FDA Orange Book</i>	1984-2010	Comprehensive list of patents for FDA-approved drugs.
Lawsuits Filed <i>Derwent Litalert</i>	1984-2010	Covers 50-70% of all U.S. patent lawsuits (most years), includes filing dates, settled cases.
Trial Decisions <i>LexisNexis</i>	1984-2012	Complete opinions include decisions, decision dates, firms, Paragraph (iv) info, patent numbers.
<b>Additional Sources:</b>		
ANDA Filings <i>FDA</i>	3/2/2004-present	Comprehensive list of ANDAs, including non Paragraph (iv) cases.
FTC (2002)	1984-2000	Comprehensive list of Paragraph (iv) cases 1992-2000, includes drug and firm names.
Panattoni (2011)	1984-2007	Sample of noteworthy Paragraph (iv) cases
P-(iv) ANDA Approvals <i>FDA</i>	5/5/1987-7/24/2009	Sample of letters to generic firms regarding successful Paragraph (iv) ANDAs, includes 180-Day Exclusivity, patent type and P-(iii) certifications.

**Note:** We cross check all sources and identify the earliest Paragraph (iv) filing per drug.

### 3.2.1 Paragraph (iv) Patent Filings and Litigation Decisions

We start by capturing all drug patents listed in annual issues of the Patent and Exclusivity Addendum to the FDA Orange Book from 1985 to 2010, including those that have expired or been delisted.<sup>5</sup> This yields 3,219 distinct patents. On average, a brand drug, which corresponds to a unique New Drug Application (NDA) number, has five patents listed in the Orange Book over its life span. We also record all drugs and firms connected to these patents.

We search for pharmaceutical litigations by patent number, firm name, and drug name. We first match our Orange Book information to filed cases in the Derwent Litalert data. Available through WESTLAW, these data include firm names and litigated patents for patent lawsuits during 1975-present. Federal courts must report all patent lawsuits to the U.S. Patent and Trademark Office, and the Derwent data are captured from these filings. It is appropriate to think of Derwent data as a random sample with a rate of sampling that varies across time, in most years 50-70% of all filed cases (Turner et al. 2013). Derwent data do not include drug names or, more importantly, decisions.

To find decisions, we use our Orange Book and Derwent information to search for written opinions in LexisNexis. This archive includes all opinions in district court cases that are recorded by the Federal Reporter. Opinions always include decisions, decision dates and courts, and nearly always include correct patent numbers and firm names. In pharmaceutical cases, they typically include drug names and information on whether the case pertains to a Paragraph (iv) ANDA filing. LexisNexis records also reveal whether there is an appellate decision in the case. Opinions do not typically include filing dates and often do not include information about the 180-Day Exclusivity. We match Derwent filings

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<sup>5</sup>The 1986 OB is not available and the 1984 version did not have the patent and exclusivity addendum. However, patents showing in immediate subsequent years reflect the patents listed in the years missing.

to LexisNexis opinions so that filing dates may be matched to other variables. We also use filings to determine the identity of the first generic firm sued.

We supplement this sample of lawsuits by searching several additional sources. First, we use a sample of letters from the FDA to generic firms discussing their Paragraph (iv) ANDAs.<sup>6</sup> The sample spans May 05, 1987-July 24, 2009 and includes 373 letters representing 200 brand-name drugs.<sup>7</sup> These letters record the listed patents for a particular drug and which ones face Paragraph (iv) certifications. Additionally, 198 of the letters include information on the outcomes of litigation. Comparing these letters to our Derwent and LexisNexis records, we discover 28 additional Paragraph (iv) cases, 5 of which are litigated to a decision. The letters also specify who the first filer is and if the 180-DE is at stake, so we add these variables as well.

Where possible, we also use the ANDA letters to classify patents. Specifically, we create a dummy variable for whether a patent has at least one active ingredient claim. When information on a patent's type is unavailable from the ANDA letters, we use a separate classification of patents as active ingredient patents (or not) based on language in the USPTO patent documents themselves.<sup>8</sup> We check our patent classification accuracy by comparing, for all patents classified in the ANDA letters, our claims-based classifications versus the letter-based classifications. We misclassify just three out of 953 patents in the ANDA letters (0.3%), giving us confidence in our method.<sup>9</sup>

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<sup>6</sup>These letters are archived in the FDA Biosciences Library in Silver Spring, MD. We thank Lee Hu, who made scanned .pdf files of these letters, for providing them to us.

<sup>7</sup>We combine different formulations and dosages under one drug name.

<sup>8</sup>Specifically, for each patent, we record the first noun in each claim. If at least one patent claim has as its first noun "compound" (or derivatives of this word) or simply reproduces a chemical formula, we classify the patent as an active ingredient patent. We compare the patent classification from the patent documents against the classification available from the letters and our classification accuracy is 99.68%.

<sup>9</sup>ANDA letters also sometimes include information about Paragraph (iii) certification filings for a subset of listed patents. Of the 953 patents in these letters, 5% face Paragraph (iii) certifications. Most patents facing Paragraph (iii) (79%) have an active ingredient claim.

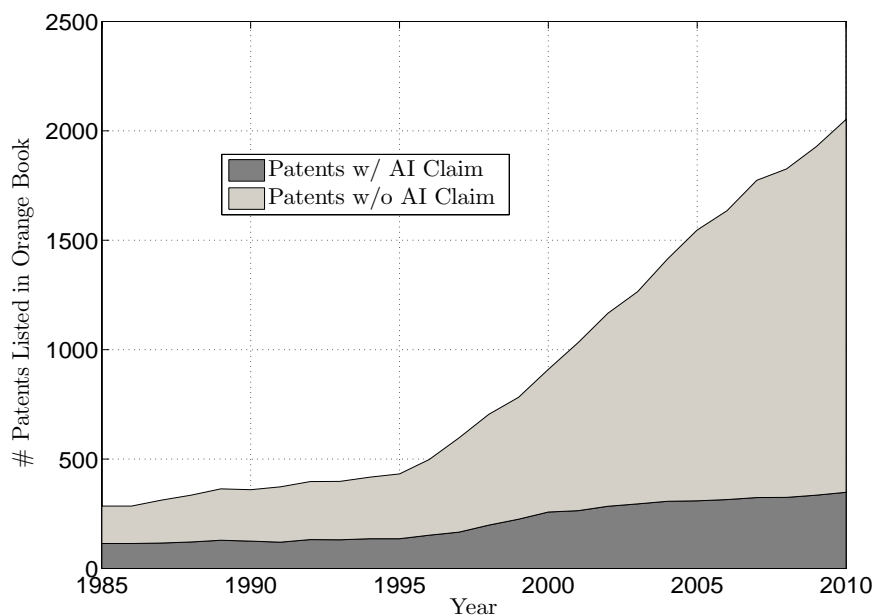


Figure 3.1: *Trend in # of Patents in Orange Book from 1985-2010.*

**Note:** The patent trends reflect cumulative patents showing in a given year according to every annual edition of the OB.

Figure 3.1 presents the total number of patents listed in each edition of the Orange Book, as well as the number of those patents that have at least one active ingredient claim. The proportion of patents claiming an active ingredient has steadily declined as the total number of listed patents has increased substantially.

The number of patents listed in the Orange Book closely tracks the growth in sales from 1985 to 2010. Figure 3.2 shows annual sales (in 2010 U.S. billions) for the top one thousand drugs according to IMS sales data over this period.<sup>10</sup> The rapid increase in sales during this period keeps the ratio of patents to sales fairly steady. The low of 4.8 patents per billion dollars of sales occurs in 1995, while the high of 8.7 occurs in 1985. Only in recent years has the ratio of patents to sales nears the highs observed in the 1980s.

<sup>10</sup>We use the U.S. GDP deflator to adjust sales, and other dollar values to reflect 2010 current dollars.

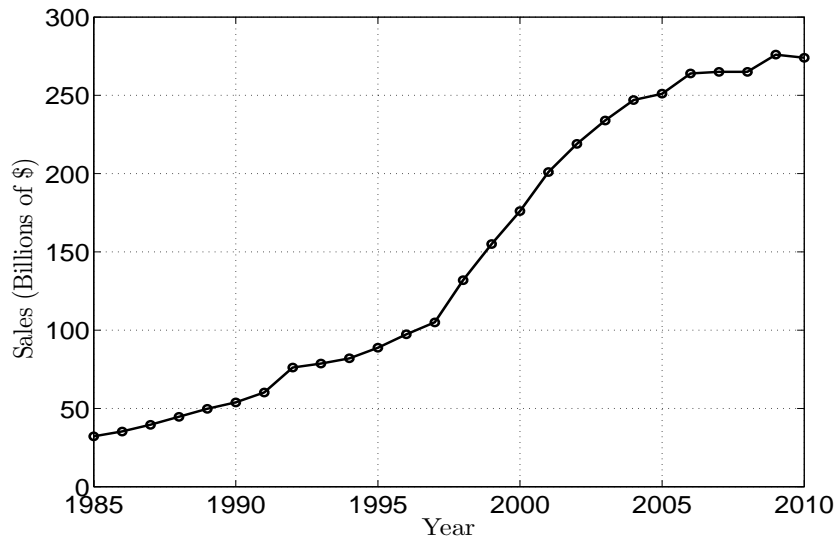


Figure 3.2: *Trend in Annual Sales from 1985-2010.*

**Note:** These numbers relate to total annual sales for top 1000 drugs listed in IMS. All dollar figures are standardized to 2010 US dollars.

We calculate the number of litigated Paragraph (iv) cases in each year from 1985-2010 using information from LexisNexis, Derwent, FTC (2002), FDA ANDA (iv) filings, Paragraph (iv) letters, and ANDA (iv) approval letters (see Table 3.1). Perhaps unsurprisingly, the frequency of these litigations, which represent generic entry attempts, closely tracks the trends in sales and patenting. Figure 3.3 provides the trend in these litigations, along with the frequency with which the litigation continued to a decision.<sup>11</sup>

For these trends, the reference year is when lawsuit is initiated. Hence, for litigations that result in a decision, the observations are counted for the same year when

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<sup>11</sup>This trend counts only the first time a drug (as per our definition of drug) faces a Paragraph (iv) filing.

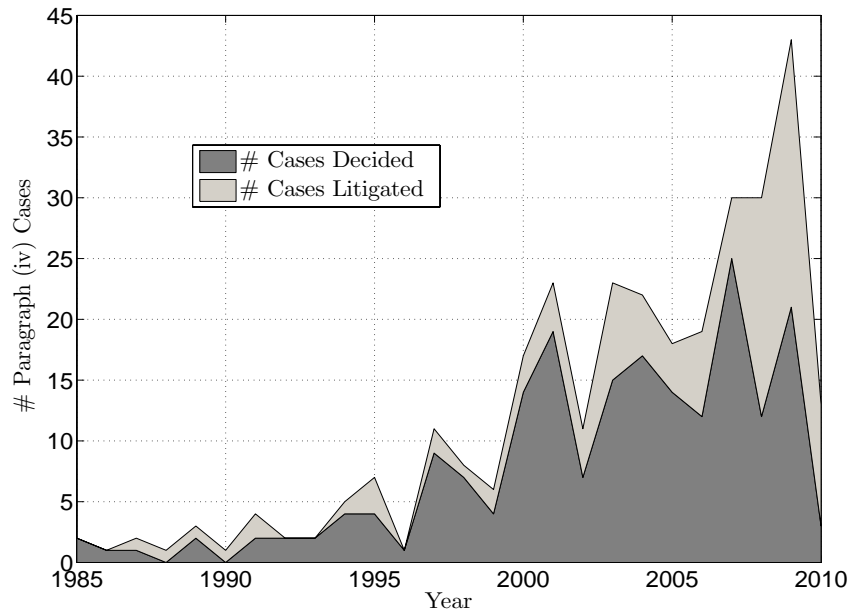


Figure 3.3: *Trends in Paragraph (iv) Litigations and Decisions from 1985-2010.*

**Note:** Paragraph (iv) challenges count the first challenge per drug, where different dosages and formulations of the same drug-name are treated as one. “Year” is the year lawsuits are filed.

they are filed, not the year they are decided. This also makes it easier to see the fraction of cases that are likely settled (i.e., litigated minus decided cases).<sup>12</sup> The widening gap between total litigations and decisions suggests firms have been more inclined to settle cases rather than litigate them to a decision (Greene and Steadman, 2010).

In total, 301 drugs that face Paragraph (iv) certifications are challenged in court and 159 of these challenges are litigated to a decision. We compare our data capture to the FTC (2002) publication on “Generic Drug Entry Prior to Patent Expiration.” The FTC paper includes a comprehensive list of drug and firm names for 104 Paragraph (iv) ANDAs during 1992-2000, 75 of which are litigated to a district court decision. Our matching of

<sup>12</sup>The drop in 2010 is because many of the cases beginning in this year are not yet resolved during the collection of our data.

Orange Book patents to Derwent and LexisNexis records misses just one of the 75 cases (we add this case).<sup>13</sup> This gives us confidence that our complete data set includes the disproportionate majority of litigations during 2000-2010 as well.

Generally, the trends we observe in the industry from 1985 to 2010 suggest that generic firms' attempts at entering are closely related to sales. These trends also suggest up-ticks in patenting and litigation in the late 1990s, when the ratio of patents to sales is the highest. Although we are hesitant to attribute the clear increase in generic challenges on brand patents to a single event, it is worth noting that *Mova Pharm. Corp. v. Shalala* [955 F. Supp. 128 (D.D.C. 1997), aff'd, 140 F.3d 1060 (D.C.Cir. 1998)], which invalidates the successful defense requirement, occurs during this time frame. The implication of this decision is that a first ANDA (iv) applicant can prevent entry of another generic firm even when the first one has not succeeded in a litigation case but the second generic has (Korn et al. 2009). Thereby, this decision strengthens the power of the 180-DE rights.

There are also other factors that may have contributed to the acceleration of dynamics in this industry in the mid 1990s. Starting 1992, the Prescription Drug User Fee Act (PDUFA) accelerates the approval of drugs, which at that point are already in the review pipeline. Hence, in 1996 the approval of NCEs drugs jumps from the 22 annual average, to 53 in that single year, 38 in 1997, and 32 in 1998, before coming back down to the average in 2001. Other factors include a restructuring of private health care plans in the same era which expanded to include coverage over prescriptions. The combination of these factors translates into higher drug sales and subsequently into more generic challenges.

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<sup>13</sup>FTC (2002) also states that there were 26 Paragraph (iv) decisions during 1984-91 but does not record drug or firm names. Our matching of Orange Book patents to Derwent and LexisNexis records, plus the ANDA letters, captures 16 decisions during this period.



### 3.2.2 Sample Selection

We now define the two samples we analyze, the Basic Criteria and the Announcement Criteria samples. Both criteria use the same definition of a drug, treating different formulations or dosages as one. Paragraph (iv) decisions where first generic entry is at issue are the focus of both samples. They differ with respect to the criteria that are used to omit decisions and with respect to the timing of the event used to estimate the effects of litigation outcomes.

#### *Basic Criteria Sample*

Our primary goal is to estimate the value of entry, the value of deterrence and the ratio of the two. Hence, our ideal data are litigation decisions where there is a status-quo monopoly and where entry is on the line. Since we rely on stock-market returns and an event study approach to estimate these values, we focus on public firms.<sup>14</sup>

Our Basic Criteria sample reflects these goals. Among the 159 Paragraph (iv) decisions, we first restrict attention to cases where there was no generic entry, including the subject drug's active ingredient prior to the district court decision. We rely on the FDA Orange Book and its website (Drugs@FDA) to determine when any generic entry occurs. We also check with Factiva and LexisNexis news sources if a generic firm launches at risk, during the litigation proceeding and before the district court decision, due to the expiration of the 30-month stay. A launch at risk arises when the generic firm could face infringement damages to the brand firm because the case has not been resolved. Only one case is eliminated due to a generic launching at risk (Neurontin). One more case in this group is a non-standard Paragraph (iv) because its patents are not listed in the Orange Book at the time of litigation (Augmentin). In total, we eliminate 44 cases where

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<sup>14</sup>We thank Professor Joseph Miller at the University of Georgia Law School for his advise in interpreting some cases to clearly determine that entry is on the line.

monopoly in the active ingredient market is not the status-quo as of the date of the respective district court verdict.

Next, we drop 6 cases because they are not standard Paragraph (iv) cases. Four of these involve issues about patent extensions, one involves a use code associated with the patent, but not the patent itself. The sixth case (Nolvadex) involves the generic firm (Barr) facing the threat of being shut down by the FDA.

We observe multiple cases on the same active ingredient, or the same patent(s). In these scenarios we use the first of the two. Hence, we drop 9 cases due to this reason. In total we drop 59 cases because they do not strictly conform to monopoly being the status-quo or entry being clearly on the line. This leaves us with potentially 100 clean cases to do the event study with.

However, while applying the event study routine, we drop 7 cases. Two cases have overlapping events and 5 cases do not have public information for the firms involved at the time of the district court decision. Hence, in the end, we have 93 final drug observations, with at least one public firm, to include in our Basic Criteria sample for the event study.

Next, we match the firms involved in Paragraph (iv) decisions with their stock returns from CRSP. We use SDC Platinum by Thomson Financial Securities Data to track mergers and acquisitions (M&A).<sup>15</sup>

Note that the “no generic entry in the ingredient market prior to the litigation decision” rule is less strict than a rule where only former NCE drugs are included. Indeed, our sample includes 20% of drugs that never had NCE status. A drug with NCE status clearly inherits monopoly status from its approval because the FDA would not approve any generic version during this five-year exclusivity.

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<sup>15</sup>SDC covers all corporate transactions from 1962-present. Prior to 1992 it reported cases involving at least 5% of the ownership of a company where the transaction was valued at \$1 million or more. After 1992, deals of any value are reported.

A drug that faces potential first generic entry through the Paragraph (iv) process without ever having NCE status arises when a product is approved for the very first time prior to 1984, when the NCE exclusivity is not yet established. In addition, as new uses are discovered for these molecules, the new form of the drug would not receive NCE status, but it could still receive other exclusivities that allow the brand sponsor to keep a monopoly status. These include the new drug formulation (NDF), pediatric exclusivity (PED) and orphan drug exclusivity (ODE), among others.

### ***Announcement Criteria Sample***

In previous work, Panattoni (2011) relies on a different methodology to estimate the effects of Paragraph (iv) decisions. Although she builds her sample from “the list of all brand drugs whose ANDA was filed before December 31, 2004” instead of the Orange Book, her “big” sample of 76 drugs involved in Paragraph (iv) decisions is similar to ours for the same time window (1984-2007) except for 7 Paragraph (iv) decided cases that we observe but are not in her sample. In addition, there are 2 cases in her sample for which we observe earlier decisions than what she observes.

To benchmark our work against hers, we construct a second sample using (almost) the exact same criteria as hers. The construction of this sample, prior to dropping any cases in the event study routine, is as follows. The criteria is identical to Panattoni (2011) for the capture of decisions involving publicly-traded brand firms, so our Announcement Criteria sample includes all 37 decisions that Panattoni studies. Moreover, our Announcement Criteria sample also includes an additional 13 decisions from Panattoni’s “big” sample, 1984-2007, where the brand firm is private but the generic firm is publicly-traded.

Lastly, we include 38 decisions from 2008-2012. However, 3 cases drop during the event study routine due to overlapping events and 3 cases because there was no public

information on the firms at the time of the verdict. Hence, in the end we have 82 drug-cases, with at least one public firm, to include in the Announcement Criteria sample.

### *Differences Between Basic Criteria and Announcement Criteria Samples*

The Announcement Criteria differs from our Basic Criteria in several ways. First, it uses as event dates the dates that decisions are *announced* in publications. In doing so, it omits decisions without an announcement.

Second, the Announcement Criteria does not adopt the “status-quo monopoly, entry-on-the-line” condition that forms the basis of the Basic Criteria. On one hand, the Announcement Criteria includes cases where there was generic entry in the ingredient market prior to the litigation decision. There are 9 of these decisions in the 1984-2007 data considered by Panattoni (2011) and 7 for the 2008-2012 window. In the other 66 cases, monopoly is the status-quo as of the district court decision date.

Third, Panattoni (2011) drops 10 additional cases, from her “big” sample, involving foreign firms whose shares are, in fact, traded on U.S. exchanges.<sup>16</sup> The Basic Criteria includes such firms. This may be due to our use of M&A data to track firms and their subsidiaries.

Fourth, the Announcement Criteria also drops 8 cases due to confounding events such as hire of new management, earning reports etc. The Basic Criteria does not drop these events in general because no other Paragraph (iv) lawsuit is decided in the same event window. The only case that we drop in this respect is (Nolvadex) because the generic firm faced threats of being shut down by the FDA. The Announcement Criteria also drops one additional case where the brand licenses the patent from another firm. The Basic Criteria includes this observation because the district court decision affects the brand in the same way as if it owned the patent.

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<sup>16</sup>All the cases dropped for the 1984-2007 window and the reasons for doing so are outlined in Table 1 of Panattoni (2011).

Moreover, the Panattoni(2011) final event sample is not entirely a sub-sample in the Basic Criteria sample but it is a sub-sample of the Announcement Criteria. Our Basic Criteria sample includes 27 of the 37 drug cases in Panattoni’s event sample. The 10-drug mismatch is due to 2 cases for which we find earlier district court decisions than the decision dates Panattoni observes. Seven cases had generic entry in the active ingredient market prior to the respective district court decision. Lastly, one case is not a standard Paragraph (iv). This case refers to Augmentin, where the litigated patents were not listed in the FDA Orange Book at the time of litigation. <sup>17</sup>

In sum, from the 93 final drug cases in the Basic Criteria sample, 33 of them are not in the Announcement Criteria sample. In contrast, 21 out of the 82 final drug cases in the Announcement Criteria are not in the Basic sample. Hence, this comparison yields 61 drug cases that are in both samples.

### **3.2.3 Descriptive Statistics**

In this subsection, we provide descriptive statistics for two different units of observation. The first is the case level, in which each lawsuit represents one observation. The second is the event level, in which there is an observation for each participant in the litigation.

Consider the following example. In the lawsuit concerning the drug Detrol, Pfizer is the plaintiff and Teva is the defendant. Since these firms are both involved in the same case, we treat this as one case level observation. Because both Pfizer and Teva are public firms, this case yields two event level observations, one for each firm.

#### ***Case Level***

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<sup>17</sup>This technicality translates into the FDA potentially being able to approve a generic ANDA even if the patents hold up in court. However some generic firms may not market under these circumstances if the generic firm wants to avoid paying damages in the event the patents hold up. These are cases filed under section 357 and not section 355 Paragraph (iv).

Table 3.2: *Descriptive Statistics at Drug-Observation Level, Paragraph (iv) Cases, 1984-2012*

	<b>Basic Criteria</b>		<b>Announcement Criteria</b>	
<b>Lawsuits</b>	159			
Litigated to a Decision-Final Sample	93	58.49%	82	51.57%
<b>Litigated to a Decision-Final Sample</b>	Mean	SD	Mean	SD
Drug Sales-Yr Lawsuit (millions)	1,020.69	1,277.42	1,085.82	1,343.72
Blockbuster (top 25)	0.32	0.47	0.34	0.48
At Least One Compound Patent	0.54	0.50	0.39	0.49
Drug Had NCE Status Prior to Litig	0.82	0.39	0.85	0.36
Number of Patents	1.87	1.34	1.89	1.35
Two Public Firms	0.61	0.49	0.55	0.50
Brand Wins	0.57	0.50	0.50	0.50
District Decision is Appealed	0.72	0.45	0.81	0.40
<b>Time Relative to District Court Decision</b>				
Youngest Patent-Life Left Yrs	6.18	3.76	6.75	4.05
Oldest Patent-Life Left Yrs	4.95	4.19	5.79	4.34
Since NCE expired Yrs*	5.28	2.83	5.96	3.35

**Note:** All the statistics are relative to the final sample (N= 93 and 82) respectively, except for the ‘Since NCE expired Yrs’ statistics which are relative to the NCE drugs (76 and 58 respectively). We report ‘Drug Sales’ averages for the year the litigation begins. This is typically also the year when sales begin to peak for many drugs.

Table 3.2 shows descriptive statistics at the case level. The second and third columns report the mean and standard deviation for our Basic Criteria sample. The fourth and fifth columns report these same statistics for the Announcement Criteria sample.

The average drug in the Basic Criteria sample realized \$1,020.69 million in sales the year the lawsuit commenced and about one in every three drugs are blockbusters (top-25 in

sales). The Announcement Criteria sample includes slightly higher sales drugs with an average of \$1,085.82 million. The average lawsuit includes about two patents for both samples. Moreover, one in every two cases includes an active ingredient patent, for both samples. For the Basic (Announcement) Criteria, 61% (55%) of the cases, the generic and the brand are both public firms, the rest of the cases only one party is public. The brand wins about 57% of the time in the Basic sample and about 50% of the time in the Announcement sample. Cases in the Announcement sample are appealed more often (81%) compared to the Basic sample (72%).

In Table 3.2, we also look at the time of patent expiration relative to when the district court issues its verdict. The last patent to expire (youngest patent) typically expires 6.18 years after the verdict is issued. The first patent (oldest patent) expires on average 4.95 years after the verdict. In addition, the verdict is reached 5.28 years after the expiration of the NCE exclusivity. This means that the average drug enjoys just over 10 years of monopoly despite potentially facing generic challenges after its NCE exclusivity expires. In addition, the statistics on when patents expire suggests that the average case has about 5.6 years of monopoly on the line in addition to the average 10.28 years before a district court verdict. For the Announcement Criteria sample, the average case has 6.3 years of additional monopoly on the line after the district court decision is issued.

### ***Event Level***

The 93 cases in our Basic Criteria sample yield 82 brand events and 68 generic events, one observation for each public firm involved in these cases. The Announcement Criteria sample includes only cases that generated an announcement, a total of 82 cases, generating 67 brand events and 60 generic events. These two samples form the basis for our event study.

Table 3.3: *Descriptive Statistics, Paragraph (iv) Litigation Events, Public Firms in Cases Litigated to a Decision (1984-2012)*

	Basic Criteria		Announcement Criteria	
	Mean	SD	Mean	SD
<b>Brand Firm Events</b>				
Drug Sales-Yr Lawsuit (millions)	985.97	1,297.38	1,045.83	1,401.41
Firm Employees (thousands)*	63.94	37.62	59.75	41.13
Firm Revenue (billions)*	29.25	19.51	27.40	20.61
Blockbusters	0.32	0.47	0.30	0.46
Number of Patents	1.85	1.35	1.91	1.40
At Least One Compound Patent	0.51	0.50	0.36	0.48
Brand Wins	0.55	0.50	0.49	0.50
Appeal	0.71	0.46	0.76	0.43
Affirmed if Appealed	0.60	0.49	0.59	0.50
Number of Events	<b>82</b>		<b>67</b>	
Number of Unique Firms	<b>26</b>		<b>27</b>	
<b>Generic Firm Events</b>				
Drug Sales-Yr Lawsuit (millions)	1,100.46	1,164.47	1,166.31	1,223.42
Firm Employees (thousands)*	22.59	27.62	19.71	26.33
Firm Revenue (billions)*	8.44	11.84	7.20	10.54
Blockbusters	0.37	0.49	0.40	0.49
Number of Patents	2.02	1.49	2.02	1.48
At Least One Compound Patent	0.54	0.50	0.43	0.50
Generic Wins	0.41	0.50	0.50	0.50
Appeal	0.75	0.44	0.87	0.34
Affirmed if Appealed	0.63	0.49	0.67	0.47
Number of Events	<b>68</b>		<b>60</b>	
Number of Unique Firms	<b>18</b>		<b>15</b>	

**Note:** All statistics are relative to the respective number of events, except for the one marked with a star (\*) which are 2 of observations short for brands (3 for the Announcement sample) and 5 observations did not have this information for the generic group for the Basic sample (7 for the Announcement sample).

Table 3.3 highlights similarities and differences of brand and generic events for both samples. In both samples, brand firms are three times as large as generic firms on average (by employees and by revenue). The total number of brand firms in the Basic sample is 26



(over 3 litigations per firm) and the number of generic firms is 18 (close to 4 litigations per firm). The Announcement Criteria sample has 27 brand firms and 15 generic ones. More importantly, Table 3.3 shows that there is not an unbalanced selection in brand events and generic events.

The ability of our event study approach to identify the value of generic entry and brand deterrence depends crucially on there being an unpredictable component to district court decisions. That is, the district court's decision must represent a sudden and exogenous release of information to investors regarding generic entry. If the stock market aggregates this information efficiently (Fama 1970), as we assume; then, the impact of the court's decision on profitability of the firms involved in the litigation will quickly be reflected in their stock prices.

We expect that when a district court decides in favor of a brand firm, i.e., generic entry is deterred, the brand firm's stock price will increase. Conversely, when generic entry is successful, the brand firm's stock price will decrease. Figure 3.4(a) presents average returns of brand firms for those events in which generic entry was deterred. Specifically, Figure 3.4(a) plots the average return, and a 95% confidence interval for that average, for the brand firm in the ten weeks prior to the day of the decision, the day of the decision and the following three days, and the subsequent ten weeks after these days. Similarly, Figure 3.4(b) presents returns for brand firms for those events in which generic entry was successful.

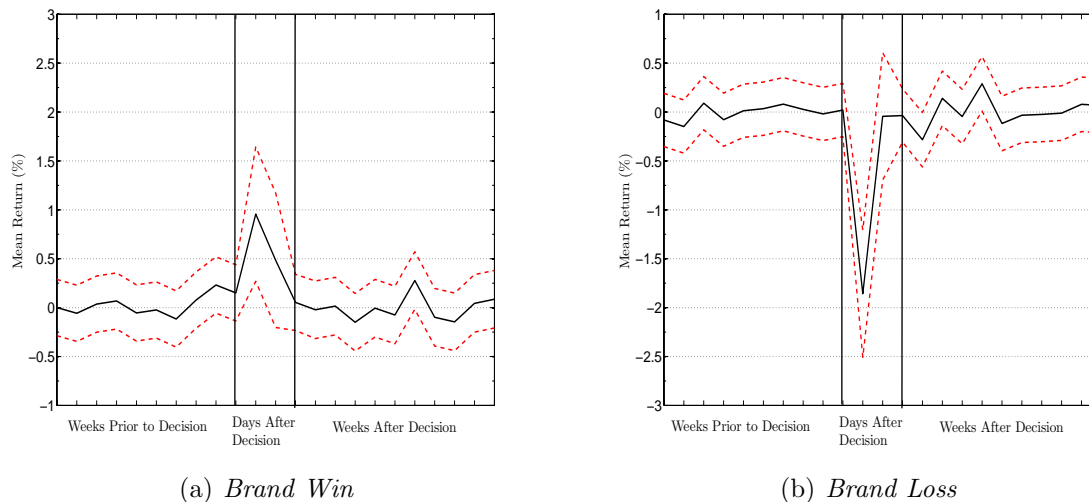


Figure 3.4: *Mean Return for Brand Firms Around District Court Decision*

**Note:** This figure shows the coefficient estimates from a regression, using the Basic sample, of brand firms’ returns on dummy variables for both the days immediately after the district court decision and the weeks prior to and following the district court decision.

Importantly, in the weeks leading up to the trial, we find no statistically significant evidence to suggest that information regarding the court’s decision becomes public in advance of its official release. We find no statistically significant variation on the day the decision, which is consistent with the decision being released after trading is halted for the day. However, for both types of events, there is statistically significant variation in returns on the day following the event. On average, on the day following the decision, brand firms’ market value increases by about 1% when generic entry is deterred and decreases by more than 1.5% when generic entry is successful. Consistent with the market efficiently aggregating information, we find no statistically significant variation in returns on the two following days, or any of the weeks after the trial. The results for generic returns follow a nearly identical pattern, and are presented in Figures 3.5(a) and 3.5(b). On average, on the day following the decision, generic firms’ market value increases by about 2.3% when they obtain the entry rights, and decrease by about 1.6% when they are denied entry. These

percentages represent only the first look at the stock market activity for the events in our study. We describe the complete empirical structure in the “Event Study Approach” section below.

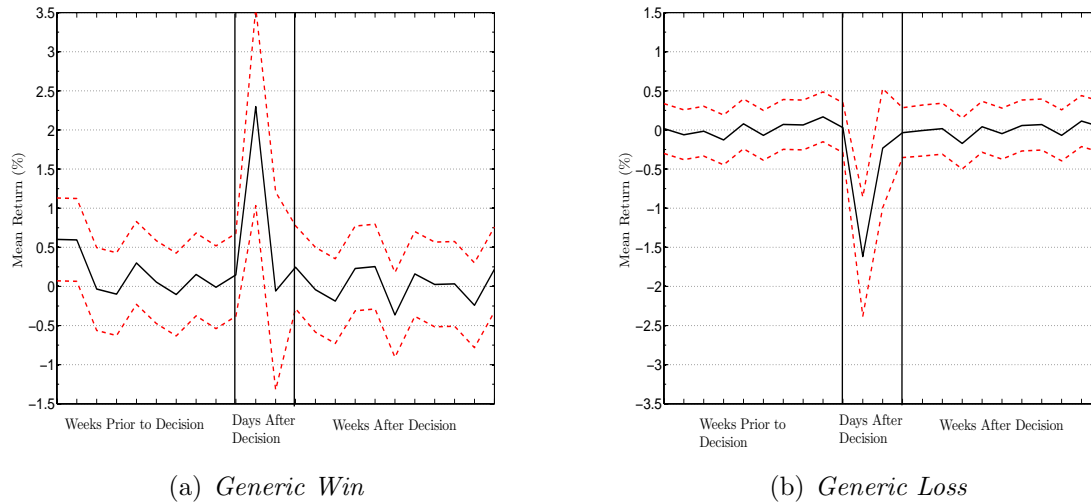


Figure 3.5: *Mean Return for Generic Firms Around District Court Decision*

**Note:** This figure shows the coefficient estimates from a regression, using the Basic sample, of generic firms’ returns on dummy variables for both the days immediately after the district court decision and the weeks prior to and following the district court decision.

Collectively, the results in Figures 5 and 6 suggest an event study approach is appropriate for measuring the value of brand deterrence and generic entry. The only statistically significant variation in returns occurs on the day following the court’s decision. Thus, the decision represents a clear and concentrated release of information on whether generic entry into the market will occur. Additionally, the speed with which the market accounts for the outcome in determining the market value of the firms involved in the litigation suggests that a two or three day event window is appropriate for the event study.

### 3.3 The Model

In this section, we introduce a theoretical model of patent litigation before proceeding to the empirical model used for the event study. This theory model serves two purposes. First, it provides insight into how the estimates from the event study relate to determinants of the value of deterrence and entry. Second, it demonstrates the biases that arise in an event study approach if an appellate process is ignored, and provides an adjustment factor to correct the estimates.

#### 3.3.1 Theory

Consider a market where a *brand firm* (B) currently operates as a monopolist and a *generic firm* (G) seeks entry. If the brand firm wishes to deter entry, it initiates litigation. If the brand firm is ultimately successful, the generic firm is not allowed to enter and the brand firm's monopoly continues. If the brand firm is unsuccessful, the generic firm is allowed to enter and the brand firm's monopoly ends.

Figure 3.6 shows a game tree mapping the outcomes of litigation. In the pre-litigation period 0, at the top of the tree, firms and investors form expectations of future payoffs prior to any decisions. Then, nature decides whether the brand or generic wins the case at the district court level. Let  $\alpha$  be the probability the brand wins. Just after the decision, in period 1, firms and investors update their expectations of future payoffs. Then, in subsequent ("appellate") review, nature determines whether the district court decision stands as unchanged or is reversed. Let  $\beta_B$  be the probability a brand win is upheld and let  $\beta_G$  be the probability that a generic win is upheld.

To conserve on notation, we do not explicitly model a decision to appeal. Implicitly,  $\beta_B$  includes the probability of all scenarios such that the district court decision is not overturned. This group includes decisions of the generic not to appeal the decision, as well

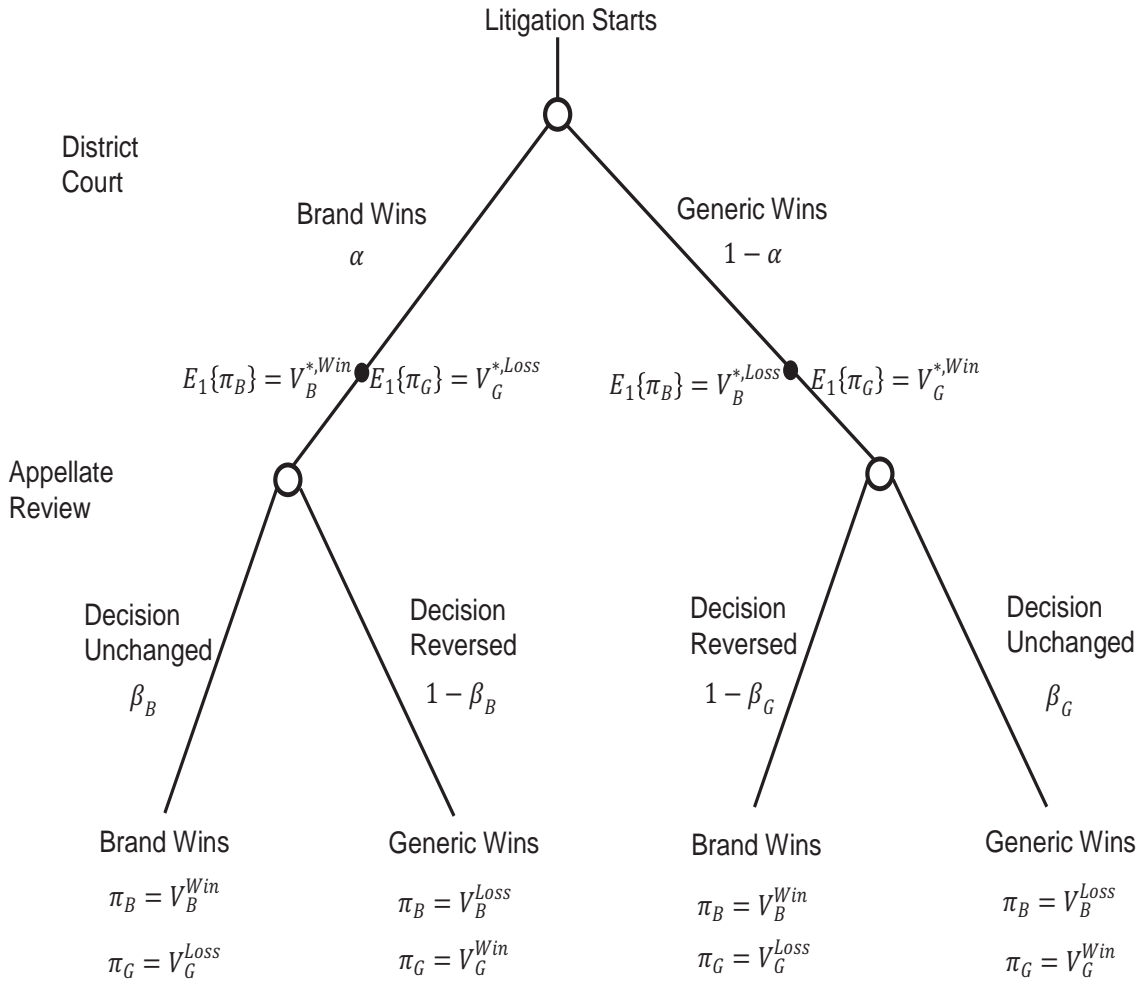


Figure 3.6: *A Model of Paragraph (iv) Patent Litigation*

**Note:** This figure shows the Paragraph (iv) resolution process. At each stage, some cases may be settled, but we use only final decisions in the event study.

as cases where the generic does initiate an appeal but the appellate case is either dismissed, settled, or decided in favor of the brand.

Let the ultimate profit  $\pi_i$  for firm  $i \in \{B, G\}$ , net of litigation costs, be the following:

$$\text{Brand Wins: } \pi_B = V_B^{Win} \quad \pi_G = V_G^{Loss}$$

$$\text{Generic Wins: } \pi_B = V_B^{Loss} \quad \pi_G = V_G^{Win}.$$

These payoffs are realized only at the conclusion of the dispute. The value of the dispute, i.e., the stakes, are not necessarily symmetric to the brand and generic. Denote the *value of deterrence* as  $V_B^{Win} - V_B^{Loss}$  and denote the *value of entry* as  $V_G^{Win} - V_G^{Loss}$ .

The main goal of this chapter is to estimate the average value of deterrence, the average value of entry and the ratio of the two. The final value of entry and deterrence are not directly observed, but can be inferred via the district courts' decisions.

Let the payoffs just upon hearing the district court decision be:

$$\text{Brand Wins District Court Stage: } E_1\{\pi_B\} = V_B^{*,Win} \quad E_1\{\pi_G\} = V_G^{*,Loss}$$

$$\text{Generic Wins District Court Stage: } E_1\{\pi_B\} = V_B^{*,Loss} \quad E_1\{\pi_G\} = V_G^{*,Win}.$$

These are shown on the tree just above the appellate review nodes. From the tree, we see that for  $i, j \in \{B, G\}$ ,

$$V_i^{*,Win} = \beta_i V_i^{Win} + (1 - \beta_i) V_i^{Loss} \tag{3.1}$$

$$V_i^{*,Loss} = \beta_j V_i^{Loss} + (1 - \beta_j) V_i^{Win}. \tag{3.2}$$

Doing a bit of algebra with these two equations above, we find, for both  $i \in \{B, G\}$ ,

$$V_i^{Win} - V_i^{Loss} = \frac{V_i^{*,Win} - V_i^{*,Loss}}{\beta_B + \beta_G - 1}. \tag{3.3}$$

Hence, the ratio  $R$  of the value of entry to the value of deterrence is independent of  $\beta_B$  and  $\beta_G$ , and is identified by values occurring just after the district court decision:

$$R = \frac{V_G^{*,Win} - V_G^{*,Loss}}{V_B^{*,Win} - V_B^{*,Loss}}. \tag{3.4}$$

Now consider the expected value of the brand firm at the very top of the tree,

$$E_0\{\pi_B\} = \alpha V_B^{*,Win} + (1 - \alpha)V_B^{*,Lose}. \quad (3.5)$$

Rearranging terms and dividing across by  $E_0\{\pi_B\}$ , we can write

$$0 = \alpha \left[ \frac{V_B^{*,Win} - E_0\{\pi_B\}}{E_0\{\pi_B\}} \right] + (1 - \alpha) \left[ \frac{V_B^{*,Loss} - E_0\{\pi_B\}}{E_0\{\pi_B\}} \right]. \quad (3.6)$$

The first term in the equation above is the market effect when a brand firm wins a Paragraph (iv) lawsuit, weighted by the probability of a brand win. Correspondingly, the second term reflects the market reaction when a brand firm loses the case. The terms in brackets are precisely what is observed using an event study approach. That is, we observe how the market changes its expectations regarding the future profitability of the firm, where  $E_0\{\pi_B\}$  equals expected profits prior to the decision, and depending on the outcome, either  $V_B^{*,Win}$  or  $V_B^{*,Loss}$  equals expected profits after the decision but before the completion of the appellate process.

Once consistent estimates of  $\frac{V_B^{*,Win} - E_0\{\pi_B\}}{E_0\{\pi_B\}}$  are obtained, it is then straightforward to calculate the average value of deterrence and entry with the assumption that  $\alpha_i$  and  $V_i^{*,Win}$  are mean independent. To do so, it is first necessary to convert the market return following the decision,  $\frac{V_B^{*,Win} - E_0\{\pi_B\}}{E_0\{\pi_B\}}$ , from a percentage into monetary terms by multiplying by  $E_0\{\pi_B\}$ . The expected absolute change in market value from a brand win, under the assumption that  $\alpha_i$  and  $V_i^{*,Win}$  are mean independent, is then

$$(1 - E_0[\alpha_i])E_0[V_i^{*,Win} - V_i^{*,Loss}].$$

Similarly, for cases in which a brand firm loses, the expected absolute change in market value equals

$$-E_0[\alpha_i]E_0[V_i^{*,Win} - V_i^{*,Loss}].$$

Subtracting the expected change in market value for a brand firm following a loss from the expected change equals

$$E_0[V_i^{*,Win} - V_i^{*,Loss}], \tag{3.7}$$

which is the expected value of the numerator of Equation (3.3).

To arrive at a consistent estimate of Equation (3.3), which characterizes the value of deterrence, it is necessary to scale Equation (3.7) by the adjustment factor that accounts for the appellate process,  $\frac{1}{\beta_B + \beta_G - 1}$ . To consistently estimate  $\beta_B$  and  $\beta_G$ , we use data on the outcomes of the appellate process, as to whether district court decisions are upheld. These estimates are presented in Table 3.4.

Table 3.4 describes three samples, All Decisions, the Basic Criteria sample, and the Announcement Criteria sample. For the full sample, just over 69% of the cases that brand firms win are appealed, but only a small portion of the initial district court brand victories are reversed (13.58%). The rest of brand victories are either affirmed, dropped in the appeal process due to a settlement or dismissal, or not appealed. Together, the rate of appeal and subsequent reversals imply a  $\beta_B = 0.86$ . Similarly, cases where generic firms win the district court decision are appealed 71.79% of the time, and are reversed 12.82% of the time, implying a  $\beta_G = 0.87$ . The adjustment factor,  $\frac{1}{\beta_B + \beta_G - 1}$ , for the full sample is then just above 1.35.



Table 3.4: *Unchanged and Reversed Decisions, Paragraph (iv) Cases, (1984-2012)*

	All Decisions		Basic Criteria		Announcement Criteria	
	N	%	N	%	N	%
<b>Litigated to a Decision</b>	159		93		82	
Brand Win	81	50.94	53	56.99	41	50.00
Brand Loss	78	49.06	40	43.01	41	50.00
<b>Brand Win DC</b>						
Appealed	56	69.14	36	67.92	33	80.49
District Decision Reversed	11	13.58	5	9.43	6	14.63
$\beta_B$	<b>0.8642</b>		<b>0.9057</b>		<b>0.8537</b>	
<b>Brand Loss DC</b>						
Appealed	56	71.79	31	77.50	33	80.49
District Decision Reversed	10	12.82	6	15.00	8	19.51
$\beta_G$	<b>0.8718</b>		<b>0.8500</b>		<b>0.8049</b>	
<b>Adjustment Factor*</b>	<b>1.3587</b>		<b>1.3233</b>		<b>1.5184</b>	

**Note:**  $\beta_i = \frac{\text{unchanged}}{(\text{unchanged} + \text{reversed})}$ , is the respective probability that the district court decision remains unchanged conditional on a possible appellate court intervention. All observations are at the drug-level instead of firm-event-level.

Thus if the appellate process were ignored, i.e., the right-hand side of Equation (3) is not scaled by  $\frac{1}{\beta_B + \beta_G - 1}$ , the estimates of the value of deterrence and entry from an event study would be biased downward by approximately 35%. As the randomness in the appellate process becomes greater, i.e., the odds of a reversal near 50%, the district court decision becomes less informative and estimates resulting from district court decisions must be adjusted substantially. Since the estimates for the two sub-samples of decisions are

similar to the full sample, we use the estimate from the full sample to adjust all our event study results.

### 3.3.2 The Event Study Approach

In an event study, the underlying assumption is that the efficient market hypothesis holds. Investors respond to an *event*, which is a firm-decision pair (e.g., “Pfizer Win,” “Teva Loss,” etc.) by changing their expectations regarding future earnings of the firm involved in the event (Fama 1970). In our setting, the efficient market hypothesis implies that each brand firm’s pre-decision stock-market value reflects Equation (3.5), and the post-decision change in their value reflects one of the two bracketed terms on the right-hand side of Equation (3.6).

The logic is that the adjustment in stock prices for the public firms involved in a Paragraph (iv) case reflects the discounted additional profits, or loss of profits, over the years after the case is decided. If the efficient market hypothesis holds, these changes in market value associated with generic entry can be quantified using an event study methodology. We estimate the effect of the district courts’ decisions for individual firms and then average these effects across four groups (two for brand and two for generic firms).

Following Salinger (1992), consider the following market model:

$$\rho_{kt} = a + b\rho_{kt}^m + \epsilon_{kt},$$

where  $\rho_{kt}$  is stock  $k$ ’s return on day  $t$ ,  $\rho_{kt}^m$  is the (compounded) return on the market index and  $\epsilon_{kt}$  is a zero-mean error. The CRSP value-weighted market index is included to separate the effect of common factors driving market returns from the effect of the litigation decision.

Now, consider a day  $T$  event. The following model permits a regression of “abnormal” returns on that day:

$$\rho_{kt} = a + b\rho_{kt}^m + \psi I_{kt} + \epsilon_{kt}, \quad (3.8)$$

where the indicator  $I_{kt} = 1$  is turned on when the market reacts to the event  $t = T$  and is 0 otherwise. We estimate our model for event  $k$ , by ordinary least squares regression.

Following Panattoni, we use a window of 271 trading days which covers the day before the event and back,  $t = [-271, -1]$ .<sup>18</sup> However, we consider a three-day event window,  $t = [0, 2]$ , in order to capture the stock market’s reaction the day of the event and two days after. Notice that Figures 3.4 and 3.5 support this choice, as all statistically significant variation in stock prices is resolved the day following the decision.<sup>19</sup>

We repeat this estimation procedure for each event involving a generic or brand firm that is publicly traded. This yields an estimate,  $\hat{\psi}$ , of the change in market value due to the district court outcome for each firm ( $\frac{V_B^{*,Win} - E_0\{\pi_B\}}{E_0\{\pi_B\}}$ , in the case of a brand win). We refer to this estimate,  $\hat{\psi}$ , as the estimated cumulative abnormal return ( $\widehat{CAR}$ ). The “average cumulative abnormal return” (average  $\widehat{CAR}$ ), used to construct the average value of deterrence and entry as discussed above, is then estimated for events in the following four categories: brand wins, brand losses, generic wins, generic losses. Like Salinger (1992), we construct an asymptotically normal test statistic to test the null hypothesis. For each of the four categories of events the null hypothesis is that a litigation decision has no effect on firm value, i.e., the average cumulative abnormal return is zero.

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<sup>18</sup>If we have between 150 and 200 trading days’ worth of data; then, we estimate the model with the data and include the event. If we have fewer than 150 trading days’ worth of data; then, we drop the event.

<sup>19</sup>We also use two and four day windows and find nearly identical results.

## 3.4 Results

We first compute the value of the verdict at the district court decision and then apply an adjustment factor to consider cases that are reversed in the appellate process.

### 3.4.1 Main Results

We use daily returns and the CRSP value weighted index for market performance in our event study regressions, both excluding dividends.<sup>20</sup> We compute the dollar effect of litigation by multiplying the average impact ( $\widehat{CAAR}$ ) times the firms' average value (shares outstanding times price per share). We use firms' values as of the day prior to the event,  $t = [-1]$ .<sup>21</sup>

From the entry and deterrence values in both samples, we compute the ratio of the two. In both samples, the value of entry is highly asymmetric to the value of deterrence. As Table 3.5 shows, this ratio is 19.35% in our Basic Criteria sample. In comparison, this ratio is even more asymmetric in the Announcement Criteria sample (14.63%). This difference is mainly due to the multiple cases in one sample and not in the other. Average sales in both samples are close to each other. The number of firm events is also close; 150 in the Basic sample versus 127 in the Announcement sample. Moreover, we also estimate the Announcement sample, not in the table, using the district court date as a reference instead of the announcement date and the differences still persist due to the mutually exclusive cases.<sup>22</sup>

The two samples yield similar event estimates at the percentage level (CAAR) for the group of cases when brand firms win. These values are 2.08% for the Basic sample and

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<sup>20</sup>We also verify the regressions including dividends, but the basic results do not change.

<sup>21</sup>We compute our estimates by coding a manual routine and also check these results using EVENTUS, a canned routine available by Wharton Research Data Services (WRDS). EVENTUS confirms our choice of days in the event window based on the days that have individual significant effects.

<sup>22</sup>In 76% of the cases the difference between announcement and district date is zero or one case being 6 days apart, the rest are 4 or less days apart.

Table 3.5: *Event Study Results*

	Brand Firms (i=B)		Generic Firms (i=G)	
	j=WIN	j=LOSE	j=WIN	j=LOSE
<b>Basic Criteria</b>	<i>N=45</i>	<i>N=37</i>	<i>N=28</i>	<i>N=40</i>
CAAR (z-stat)	2.08%*** (3.35)	-2.43%** (-2.43)	3.13%*** (3.14)	-1.63%** (-2.37)
Decision Impact ( $V_i^{*,j} - E[V_i^*]$ )	\$1,616.57	-\$1,269.29	\$312.76	-\$245.67
Value of District Court Outcome ( $V_i^{*,Win} - V_i^{*,Lose}$ )	\$2,885.86		\$558.43	
Value of Dispute ( $V_i^{Win} - V_i^{Lose}$ )	\$3,921.02		\$758.74	
Value of Entry as % of Value of Deterrence			<b>19.35%</b>	
<b>Announcement Criteria</b>	<i>N=33</i>	<i>N=34</i>	<i>N=30</i>	<i>N=30</i>
CAAR (z-stat)	2.53%*** (3.79)	-4.18%*** (-3.10)	4.31%*** (3.49)	-1.59%** (-2.07)
Decision Impact ( $V_i^{*,j} - E[V_i^*]$ )	\$1,961.26	-\$1,968.92	\$368.63	-\$206.31
Value of District Court Outcome ( $V_i^{*,Win} - V_i^{*,Lose}$ )	\$3,930.18		\$574.94	
Value of Dispute ( $V_i^{Win} - V_i^{Lose}$ )	\$5,339.94		\$781.17	
Value of Entry as % of Value of Deterrence			<b>14.63%</b>	

**Note:** The percentage estimates, in bold, reflect equation (3.4). The respective significance levels are: 1%(\*\*\*) ; 5%\*\* ; 10%(\*).

2.53% for the Announcement sample. Similarly, both samples have similar results for the generic defeats group (-1.63% vs. -1.59%). However, there are some differences between the two samples across the brand-lose and generic-win groups. For the generics-win group, there are seven cases in the Announcement sample not in the Basic sample that have high individual effects.<sup>23</sup> The likely explanation is that these drugs represent a high earnings potential for smaller than average generic firms. For the brand-lose group, there are twelve cases in the Announcement Criteria not the in the Basic Criteria sample. However, there

<sup>23</sup>These cases are: Mircette, Naprelan, Protonix, Temodar, Tiazac, Ultram, Zyban.

are mainly three cases with high individual effects (Wellbutrin, Tiazac and Augmentin). Some explanations are that, these firms were not expected to lose the case and they did, these drugs represented a high portion of their portfolio, or a combination of the two. In addition, the pharmaceutical firms in both samples are highly dynamic and the estimation of one single event, while reflective of its individual effect, may be damped or amplified in light of many other occurrences that are not observed. However, all of our results are highly significant, in both samples.

In our Basic Criteria sample, the total value at stake for brand firms is \$3,921.02 million compared to the Announcement Criteria sample where this value is \$5,339.94 million. The average drug in our sample has about 5.6 years of monopoly at issue as of the day of the district court decision (from Table 3.2, average of oldest and youngest patents' expiration). This suggests that the average annual amount of profits at issue in our sample is \$700.18 million. This result is consistent with the average drop in annual sales, where brand sales drop by \$608 million (comparing two years prior to generic entry and two years after), upon first generic entry for a sample of 41 litigated drugs that we match to IMS sales records. For the Announcement Criteria sample, the average monopoly at issue is 6.3 years, suggesting that the average annual profits on the line for this group of cases is \$847.61 million.

The value of entry to generic firms is much smaller, in both samples, than the value of deterrence to brand firms. In the Basic sample, this value is \$758.74 million. Using IMS sales records for brand firms in litigation as above, we find that the first generic firms generate sales revenues of \$201 million in the first year that includes the 180 DE. Assuming a very small marginal cost, so that revenues closely resemble profits, these numbers suggest that there is a large amount of profits regenerated elsewhere outside the 180-DE window. In the Announcement Criteria sample, the value of entry is nearly the same, \$781.17 million on average.

## 3.5 Conclusion

Settlements between brand and generic firms in Paragraph (iv) litigations will continue to play an important role in health policy. The impact of these type of settlements has been appraised around \$35 billion over the next decade according to the FTC. The recent Supreme court decision on this matter has opened a wider door for the FTC to challenge the settlements, but has not provided a bullet-proof rule to guide the lower courts. The controversial part of brand-generic settlements is that they do not deter entry beyond the expiration of the last patent protecting a brand drug, but many delay entry compared to when a patent is declared invalid or non-infringed. Hence, the challenge for the FTC, the courts, pharmaceutical firms and researchers, is to differentiate between settlements that occur because the patent is weak (anticompetitive) and cases where the patent is strong (pro-competitive). Our classification of patents into active ingredient (AI) and patents without claiming the active ingredient combined with their performance in court can be used as a starting point. This patent classification along with our estimation of entry and deterrence values, combined with the simple rule proposed by Hovenkamp et al. (2003) can help the courts in sorting anticompetitive cases. Their rule is that if the settlement is much larger than the cost of litigation; then, brand firms should have the burden of proof.

Our event study results suggest that cases with large asymmetric payoffs, cases where the value of generic entry is very small (less than 20%) compared to the value of deterrence, have the most potential for anticompetitive settlements. In dealing with these cases, the FTC would have to consider the asymmetry of payoffs (leading to the size of the settlement), the type of patent at issue (active ingredient versus non-active ingredient), the timing of entry, and the potential generic penetration into the brand's market.

In addition to settlements, brand firms can also use spin-offs of existing drugs to game the system and obtain additional exclusivities. Yet, some of these spin-offs may be

greatly beneficial. Hence, just as with settlements, it is not clear that all of these spin-offs are pro-competitive, or that all of them are anticompetitive. Therefore, there is a need to study how brand firms use existing compounds' multiple indications and how generic firms pursue entry in these markets. Understanding these dynamics can further the goals of the Hatch-Waxman Act.



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# Appendix A

## Data Sources

### **R&D and Advertising (Compustat)**

Research and development (R&D), advertising and revenue data can be obtained directly from the Wharton Research Data Services (WR&DS). Specifically, S&P Capital IQ's Compustat North America "is a database of U.S. and Canadian fundamental and market information on active and inactive publicly held companies. It provides more than 300 annual and 100 quarterly Income Statement, Balance Sheet, Statement of Cash Flows, and supplemental data items." These data can be accessed by an account. In order to search for data specific to pharmaceuticals I use the North American Industry Classification System (NAICS) code: 325412. The variable XR&D represents annual R&D, and it is defined as follows:

*This item represents all costs incurred during the year that relate to the development of new products or services. This amount is only the company's contribution. This item includes: Software expenses and amortization of software costs. This item excludes: (1) Customer or government-sponsored research and development (including reimbursable indirect costs). (2) Extractive industry activities, such as prospecting, acquisition of mineral rights, drilling, mining, etc. (3) Engineering expense routine, ongoing efforts to define, enrich,*



*or improve the qualities of existing products. (4) Inventory royalties. (5) Market research and testing.*

Therefore, XR&D represents a general core measure of R&D that cannot be broken down into any specific projects or line of products. For more disaggregated R&D data (not used in any chapter), U.S. Census tracks R&D information in two datasets: the Business R&D and Innovation Survey (BR&DIS) and the Survey of Industrial R&D (SIR&D), but these surveys are only accessible after a formal application process.<sup>1</sup>

The variable XAD captures advertising expenses, and according to its description includes: “the cost of advertising media (i.e., radio, television, and periodicals) and promotional expenses.” Furthermore, revenue is tracked by the variable RVET, and according to Compustat’s description, it represents “the gross income received from all divisions of the company.”

### **Priority Status, Efficacy Supplements, and Accelerated/Fast-Track Approvals (FDA)**

The Orange Book does not contain whether a drug’s approval, either NDA-NCE or subsequent NDA, is classified as priority or standard. The priority classification is important because it helps differentiate drugs that are potentially more innovative than drugs approved with standard classification. This classification can be obtained via a couple of sources depending on whether the drug is a NCE or a change in indication to the original drug. The general source to observe this status is the searchable database `drugs@FDA`.

In addition, if a drug is a new molecular entity (NME), its priority status can be obtained from the annual reports on NME approvals. NMEs include NCEs but also include biologics and first-time ingredients approved before 1985. However, these annual reports are only available as far back as 1999, whereas `drugs@FDA` can be used to search beyond

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<sup>1</sup><http://www.nsf.gov/statistics/srvyindustry/about/brdis/>

that point. Another additional source is Lanthier et al. (2013), listing in their Appendix all NMEs with priority and standard approval from 1987 to 2011.

If a drug is the result of a change in indication, (i.e., second generation drug from incremental innovation) the priority status can be observed via the Efficacy Supplements. These supplements must be submitted to the FDA by the pharmaceutical company when changes to a drug's label occur. These changes can be the result of important innovations that may result in a new drug, or they can be for smaller modifications that would result only in a label change to an existing drug. These supplements are available online from the FDA as far back as 1998. Moreover, the supplements can be linked to the OB directly by a NDA identifier.

Accelerated, Fast-Track, and Breakthrough approvals offer a finer level of detail beyond the priority status. These categorizations differ from each other but also have some overlapping nature. The bottom line is that these classifications clearly indicate innovative potential for a drug beyond the more general priority status. The reports on Accelerated and Fast-Track approvals include cases as far back as 1998, while Breakthrough approvals only include a few cases as recent as 2012-2014.

### **Drug Sales(IMS)**

IMS is the leading standard data source for sales in the industry. The sales data I use correspond to wholesale figures for the top 1000 drugs for the 1985-2010 period. Since original figures are reported in nominal terms, I use the US GDP deflator (2010 as the base year) to convert nominal dollars to real dollars and compare across different years.

Moreover, the unit of observation is the drug-name level. For instance, sales are reported for Adderall, Adderall XR, and many of its other versions. If a generic version of a drug also makes it into the top 1000 drugs; then, it is included in the list. The data are only available for the year that the respective drugs make it into the top 1000 but may not

be available for the complete life-cycle of a drug. According to IMS, these sales data “are gathered either at the point of sale to pharmacies or at the point of sale to consumers.”

### **Paragraph (iv) Filings and Court Decisions**

This dataset on Paragraph (iv) challenges is the most comprehensive capture of Paragraph (iv) cases from the first cases filed in 1985 to the last decisions taken place in 2012. In particular it includes a comprehensive list of 481 drugs facing Paragraph (iv) from 1985-2010. Different dosages that result in added extensions to a drug name are not counted as different drugs. For instance, Adderall and Adderall XR represent the same drug. Out of the 481 drugs facing Paragraph (iv), 301 are challenged in court by the brand firm. I am able to observe cases decided (159) and cases that are litigated but not decided which may include a large number of settlements. However, the settlement status is not directly observed because in many cases, the settlement terms are not made public.

The collection of these data begins with every annual edition of the OB from 1985-2010 to gather a comprehensive capture of all patents ever published in the OB including patents that are now delisted or have expired. Then, using two legal search engines, Derwent and LexisNexis, each of the total 3,219 patents is searched to look for Paragraph (iv) lawsuits. Additional sources are used to gather cases litigated and not litigated from the FTC (2002), Panattoni (2011), FDA 2004-present ANDA reports and random set of ANDA (iv) approval letters (1987-2009).

### **Patent Specific Information (ANDA and USPTO)**

I classify patents into those covering claims to the active ingredient and those that protect formulations and method of use. I first rely on ANDA letters from the FDA to generic firms to make this classification. Specifically, I create a variable for whether a patent has at least one active ingredient claim. When information on a patent’s type is unavailable from

the ANDA letters, I use a separate classification of patents based on language from the USPTO patent documents directly.