

# Pharmaceutical Innovation

*Incentives, Competition, and Cost-Benefit Analysis  
in International Perspective*

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## EIGHT

### Competition between Generic and Branded Drugs

Henry Grabowski

#### I. Introduction

The United States is the country for which generic competition is the most highly developed. It is a key location of drug price competition, and there are many institutional mechanisms to encourage the utilization of generics. The Hatch-Waxman Act of 1984 was enacted with the dual objectives of facilitating entry of generic competition while preserving sufficient patent exclusivity time to incentivize drug innovation. In this chapter's next section, I discuss the provisions of the 1984 Act in some detail and review how managed care organizations encourage generic competition. Sections III through V examine findings of several economic analyses of generic competition. Section VI examines studies of effective patent life and how the 1984 Act has affected the incentives for drug innovation. Section VII focuses on the strategic responses of branded and generic firms to the 1984 Act. Section VIII provides a brief summary and discusses issues for further research.

#### II. Drivers of Generic Industry Growth

##### The Hatch-Waxman Act

The generic industry has evolved rapidly since the mid-1980s. A key event fostering the development of this industry was the passage of the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. This Act changed the regulatory criteria for U.S. Food and Drug Administration (FDA) approval of generics, thereby significantly reducing the costs and time delays of generic entry. The Act also provided benefits to innovative firms by restoring some of the patent life lost during the long regulatory period for new drugs. However, the primary impact

of the Act has been to foster greater generic competition, since the patent term extension benefits to innovators were more than offset by the increased generic competition after patent expiration that was facilitated by the law (U.S. Congressional Budget Office [CBO] 1998).

Prior to passage of the Hatch-Waxman Act, generic firms could not rely on branded drugs' safety and efficacy data for all the drugs introduced after 1962 unless this information was published in the scientific literature. In effect, these safety and efficacy data were given "trade secret" status. Hence a generic imitator had to undertake many of the same safety and efficacy tests as the innovator to gain FDA approval.<sup>1</sup> A few drug entities were able to avoid new clinical trials on safety and efficacy by relying on established studies published in the scientific literature. This procedure was called a "paper NDA" (new drug application). However, according to a 1984 House Congressional report, only about 14% of drug introductions after 1962 had sufficient published information to support a paper NDA.<sup>2</sup>

In the pre-1984 period, generic competition was mainly concentrated in the antibiotic class, which was regulated by separate monograph procedures. According to the IMS New Prescription Audit data survey, generic drugs accounted for only 19% of all prescriptions in 1984 (Pharmaceutical Research and Manufacturers of America [PhRMA] 2000, p. 69). Moreover, many large selling off-patent drugs had no generic competitors. In a study of the top 200 off-patent drugs in the early 1980s (excluding antibiotics) John Vernon and I (1986) found that only about one-third of these drugs had any generic competition at all. Moreover, those brands with generic competition typically experienced small losses in market shares to the generic brands.

The Hatch-Waxman Act dramatically altered the nature and terms of generic competition after 1984. First, the Act established an Abbreviated New Drug Application (ANDA), which substantially reduced the cost of generic entry. Second, the Act allowed generic manufacturers to conduct their testing prior to patent expiration. This allowed generics to enter the market much more quickly after patent expiration than previously.

Under the ANDA procedure established by the Act, the primary requirement for generic manufacturers is that they need to demonstrate that their drug is bioequivalent to the innovator's product.<sup>3</sup> The ANDA procedure essentially allows generics to rely on the safety and efficacy clinical trial data submitted by the manufacturer of the branded product part of the original NDA. Generic drugs must meet the same reference standards on strength, quality, purity, and identity, but they may differ in such characteristics as shape, color, and packaging.

Once a generic product meets the FDA bioequivalence requirements and other reference standards, it is assigned an AB therapeutic code, indicating that the FDA considers the generic product as therapeutically equivalent to branded product. In particular, according to the FDA, "Drug products are considered to be therapeutically equivalent only if they are pharmaceutical equivalent and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the label."<sup>4</sup> All therapeutically equivalent products are listed in the FDA's "Orange Book" (see note 3). Once a product is listed in the Orange Book with an AB equivalence rating, this means the product can be freely substituted by pharmacists for the corresponding branded product unless physicians take specific actions to prohibit such substitutions.

By establishing an ANDA process for generic approval and obviating the need to do expensive clinical trials on safety and efficacy, the 1984 Act dramatically lowered the cost of generic entry. Reiffen and Ward (2005) found that the cost of obtaining an ANDA approval in the first half of the 1990s was on the order of one million dollars. This compares to an average out-of-pocket research and development (R&D) cost for new brand drug approval in the 1990s of over \$400 million (DiMasi, Hansen, and Grabowski 2003).

Another effect of the 1984 Act was to drastically shorten the time lag between patent expiration and initial generic entry. In an analysis of several drugs that experienced generic competition between 1989 and 1993, the U.S. Congressional Budget Office (1998) found the typical time period between expiration and generic entry was one to three months. This compares to an average of three to four years for generic entry in the period prior to the 1984 Act.

### Managed Care, PBMs, and Demand-Side Factors

In the United States the substitution of a generic drug for a branded drug is well known and generally predictable. Generic substitution is regulated by state law, and all states have passed substitution laws that allow pharmacists to substitute AB-rated generics for branded counterparts, unless the prescribing physician takes specific steps to prohibit substitution, such as specifically ordering that the pharmacists "dispense as written." Strong incentives exist at present for physicians, pharmacists, and patients to utilize generic products where these products are available.

States generally have one of two types of substitution laws: permissive substitution laws and mandatory substitution laws. Mandatory substitution

states require that pharmacists substitute generic drugs for branded drugs where a generic is available and other requirements are fulfilled. Permissive substitution states allow pharmacists to substitute generic drugs for branded drugs. According to the 2003–2004 National Association of Boards of Pharmacy's *Survey of Pharmacy Law* (2004), 11 states and Puerto Rico had mandatory generic substitution laws.<sup>5</sup> In 38 other states plus the District of Columbia and Guam, pharmacists were permitted, but not mandated, to substitute generic drugs for brand name drug products. In either case, payers, physicians, and pharmacists had a strong economic incentive to substitute generic drugs for branded drugs.

According to a 2000 report of IMS Health, 82% of pharmaceutical prescriptions were reimbursed at least in part through third-party payers. Of that 82%, 13% are reimbursed by state-run Medicaid programs. Of the remaining 69%, most were reimbursed through a managed care organization, such as Health Maintenance Organizations (HMOs), Preferred Provider Organizations (PPOs), or point-of-service plans.<sup>6</sup> The U.S. Center for Medicaid and Medicare Services (2003) estimated that for the private sector, insurance covered 69.3% of prescription drug costs and 30.7% of these costs were paid out of pocket in 2001.

The government, employers, and managed care organizations have hired specialized companies called Pharmacy Benefit Managers (PBMs) to manage their drug benefit programs. PBMs now provide these benefits for more than half of the insured population in the United States (PhRMA 2000, p. 66). At the most basic level, PBMs perform electronic claims processing, provide a network of retail pharmacies and mail order pharmacy service, and offer pharmacy benefit plan design with patient cost sharing and other incentives. These activities generate costs savings to plan sponsors by reducing prescription claims-processing charges, lowering ingredient and dispensing fees, and increasing patient copayments.

Beyond those basic services, PBMs also engage in various activities designed to influence drug prescribing and dispensing (Grabowski and Mullins 1997). These activities influence the decision making process from the economic standpoint of patients, physicians, and payers. The practical effect of many of those programs is to provide strong incentives to utilize generics where available.

One of the strongest PBM approaches to encourage generic utilization involves adjusting the patient copayments so that patients will request generic prescribing and substitution. A common form of that program is the three-tiered formulary system employed by most PBMs. Under that system, generics occupy tier one and require the lowest copayment from the patient

(usually on the order of \$5.00 per prescription). Branded drugs categorized as preferred by the PBMs are in tier two and require a higher copayment than generics. Tier three mainly consists of branded drugs for which less expensive generic drugs or therapeutic substitutes are available. That is, once a generic drug enters the market, most PBM formularies automatically relegate the branded counterpart to tier three. Those drugs pay the highest copayment. As of 2002, tier three copayments could be \$30 or higher (Berndt 2002).

More stringent forms of the copayment approach are maximum allowable cost programs. Those programs require that the patient pay the full difference between the branded prescription and the normal prescription copayment. In the extreme case, mandatory generic substitution programs require that generics be dispensed or the patient receive no reimbursement at all.

PBMs also provide strong incentives for physicians to prescribe generic drugs. One such incentive arises from the PBMs' use of physician profiling and retrospective drug utilization review databases to identify "outlier" physicians; such physicians include those that more frequently prohibit generic substitution by the pharmacists (Grabowski and Mullins 1997, p. 539). Under this approach, physicians who fall outside prescribing norms are subject to "alert letters," visits from PBM personnel, and possible financial penalties. Some PBMs have capitated physicians for drug costs or instituted "withholds" based on formulary compliance.<sup>7</sup> According to PBMs, the assumption of risk for pharmacy utilization is a powerful incentive enhancing physicians' willingness to comply with formularies (Kreling et al. 1996).

PBMs also typically pay higher dispensing fees to pharmacists to dispense generics over their branded counterparts (Rubin, Hawk, and Cascade 1998). Moreover, several studies have demonstrated that pharmacists earn higher absolute margins when generics are substituted.<sup>8</sup> Hence, pharmacists also have strong incentives to dispense generics regardless of whether the drug prescription is paid for by a third party or is paid out of pocket by the patient.

Like managed care organizations, state and federal governments in the United States employ PBMs to manage pharmacy benefit programs. U.S. government agencies (e.g., Veterans' Administration, Medicaid) are among the most price-sensitive buyers of pharmaceuticals. The Medicaid program, which is jointly funded by the federal government and the states, was the first payer to adopt the maximum allowable cost program with respect to generics. In addition, many state Medicaid programs have automatic generic substitution requirements.<sup>9</sup>

The programs designed to encourage generic utilization by payers have been very effective. In terms of the overall pharmaceutical market, generic

products accounted for only 19% of all prescriptions in 1984, but this share increased to 51% in 2002.<sup>10</sup> Saha et al. (2006) found evidence for the proposition that the growth of managed care has been a key factor in the increased utilization of generic products, after controlling for various other factors affecting the demand and supply of generics.

### III. Economic Analyses of Generic Competition

A number of studies have investigated characteristics and intensity of generic competition in the United States since 1984. A distinctive pattern of generic competition has been observed (Grabowski and Vernon 1992, 2000). First, commercially significant products have experienced a large number of generic entrants within a short period after patent expiration. Second, there is a strong positive relationship between the size of the branded drug's market sales in the preexpiration period, the number of generic entrants, and the intensity of generic price competition after patent expiration.<sup>11</sup> Third, the more entrants and more intense the degree of price competition, the more rapid the erosion in the brand product market share in units to the generic firms. Fourth, an increasing number of products now are subject to patent challenges early in their product life cycle as a result of the 180-day exclusivity awarded to the generic firm that is first to file for an ANDA and successfully challenge the product in court (Grabowski 2004).

Figure 8.1, which provides some illustrative values for these trends, is based on an analysis of a representative sample of 40 oral prescription drug products that experienced first generic entry during the 1990s (Saha et al. 2006). Figure 8.1A shows there is a rapid build-up of generic competitors in the months after first entry, with an average of eight generic competitors experienced by these 40 products after 12 months' time. Correspondingly, Figure 8.1B and 8.1C show average generic prices are discounted approximately 50% below branded prices, and average generic unit shares are more than half of the unit sales (in grams) for the molecule after 12 months. The number of generics, generic discounts, and generic shares continue to increase as markets tend toward commodity status over the three-year time frame shown in Figure 8.1. A simultaneous regression model of these three variables demonstrates that the preentry market sale of the molecule is a key variable in how rapidly markets converge to their long-term equilibrium values. In addition, as discussed, the growth of third-party insurance for pharmaceuticals is an important factor in increasing the overall speed of generic penetration during the 1990s (Saha et al. 2006).

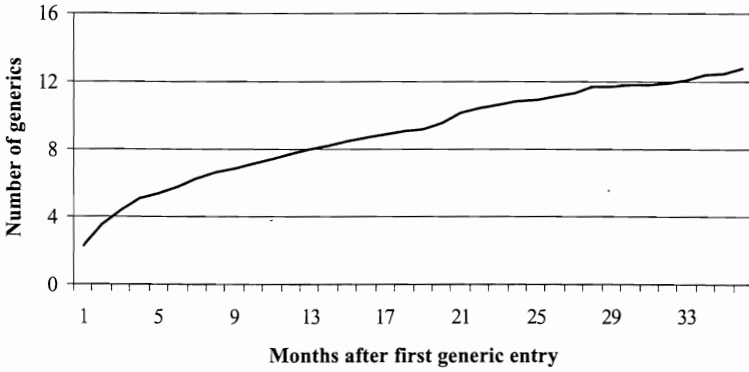


Figure 8.1A. Average number of generic drug manufacturers.

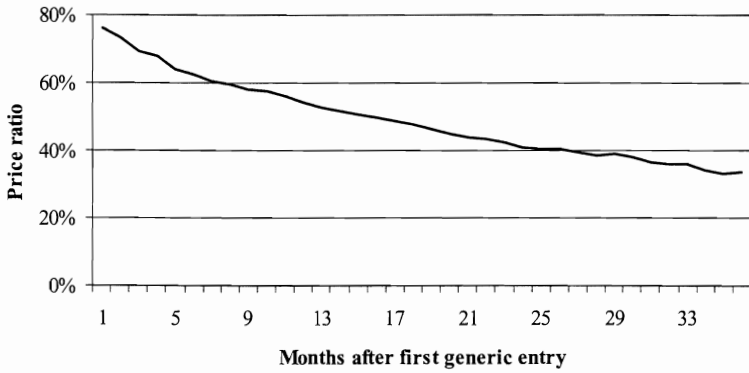


Figure 8.1B. Average generic-to-brand price ratio.

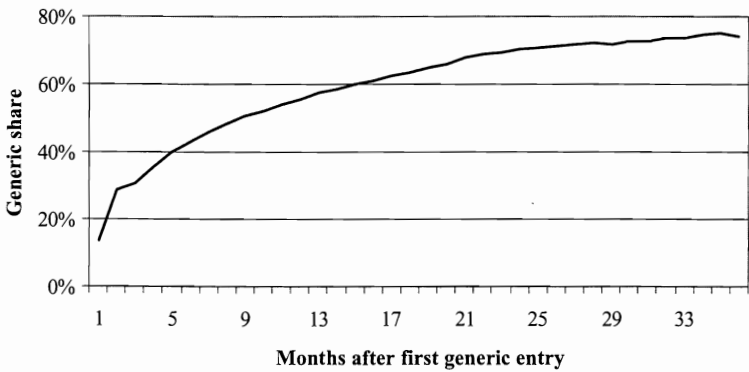


Figure 8.1C. Average generic share in gram sales. *Source:* Saha et al. (2006).



Data from the most recent launches show that, in the case of the top-selling drugs, generics are capturing most of the market within weeks of their launch. In this regard, I have examined data on the three top-selling drug products experiencing their first generic competition in 2000 and 2001 (Grabowski 2004). These products are Vasotec (enalapril), Zestril/Prinivil (lisinopril), and Prozac (fluoxetine), all of which had annual sales greater than \$1 billion. These data show that the launch of generic enalapril in August 2000 resulted in the generics obtaining 66.4% of new prescriptions just four weeks after generic launch. Generic lisinopril, launched in May 2001, acquired 84.0% of new prescriptions in four weeks. Generic fluoxetine, launched in August 2001, acquired 74.9% of new prescriptions in four weeks.

Scott Morton (1999) examined the entry decisions of generic firms. She showed that firms are more likely to enter markets in which they have some experience, for example, in form, therapy, or ingredient, and to enter markets for chronic conditions with large sales. Scott Morton (2000) found that generic entry is positively related to brand revenue and price elasticity, and negatively affected by FDA regulations. She found no evidence that brand advertising is a deterrent to generic entry.

A number of investigators dating back to Caves, Whinston, and Hurwitz (1991) have considered the response of brand firms to generic entry, and whether branded firms have pursued entry-detering strategies. There is little evidence to support the hypothesis of entry deterrence utilizing pricing or promotional strategies. First, with respect to promotional activities, the prevalent strategy is for branded firms to curtail most of their expenditures, usually beginning in the preentry period (Ellison and Ellison 2000). Second, evidence is scant on the brand firms matching generic prices, except for selective discounts to their large institutional customers (U.S. Congressional Budget Office 1998, p. 38). Most studies have found that brand firms continue to raise their prices after generic entry, but there is some disagreement in the literature about whether the impact of generics on the rate of change in prices is positive or negative.<sup>12</sup>

As the rate of sales losses for branded firms has intensified after generic entry, many brand firms have turned to the "authorized generic" strategy. This strategy authorizes a generic partner or subsidiary to rely on the branded firm's approved new drug application, and to enter at a point in time prior to or simultaneous with the first "outside" generic entrant. This strategy is particularly prevalent where the rival generic firm enjoys a 180-day exclusivity period as the result of a successful patent challenge (Siegel 2004). There are first-mover advantages to being an early entrant in the generic market (Grabowski and Vernon 1992). The authorization of

a generic entrant allows branded firms to capture some of the short-term rents associated with early entry into the market, usually in partnership with a leading generic firm.

During the 180-day exclusivity period, the presence of an authorized generic as a second generic entrant works to intensify price competition. However, an interesting policy issue is whether there are situations where an authorized generic from the branded manufacturer adversely affects the total number of generic competitors in equilibrium. (Reiffen and Ward 2006). This is an issue currently under consideration at the U.S. Federal Trade Commission.

Branded firms have employed a variety of “life cycle management” strategies, such as the introduction of new formulations and combination products and shifting a prescription product to over-the-counter (OTC) status as a means of retaining patients and preserving sales revenues in the face of patent expiration and imminent generic entry. Some firms have also tried to use provisions of the 1984 Act in patent challenges to erect legal or regulatory barriers to entry. The strategic uses of provisions of the 1984 Act by brand and generic firms are considered in the last section of the chapter.

#### **IV. Effects of Generic Competition on Total Expenditures for Prescription Drugs**

As the number of generic competitors increase for a particular prescription drug, several studies show that prices fall toward marginal cost (Reiffen and Ward 2005). In particular, generic prices can drop to less than one-third of the brand prices with 20 or more generic competitors in the market. Even for cases with significantly fewer generic competitors, generic prices typically decline to less than half the brand price within a year or more of initial generic entry (Saha et al. 2006).

Given these lower prices of generic products and the rising share of over-all prescriptions, they are a source of significant savings. In this regard, the U.S. Congressional Budget Office (CBO 1998) estimated that purchasers of prescription drugs saved between \$8 billion and \$10 billion dollars in the mid-1990s. The CBO utilized a straightforward approach in computing these cost savings. In particular, it multiplied the price difference between brand and generic drugs times the number of units dispensed generically. It utilized a representative sample of multiple source pharmaceuticals, and projected their estimates to the overall market. While this approach is subject to various qualifications, it demonstrates that the overall savings from generic products are substantial.<sup>13</sup> Furthermore, the share of prescriptions

dispensed generically has grown significantly since the mid-1990s; thus more recent estimates of savings would be much greater.

The beneficiaries of these large cost savings, at least in the first instance, are the payers for prescription drugs. Since most drugs are covered by third parties, this list includes health insurers, PBMs, employers, and the government, along with some consumers who pay out of pocket. Most employer-based prescription drug plans have a tiered system of copayments. Given the fact that almost all plans have generics in the lowest tier of copayments with a nominal copayment, some of the savings are passed on directly to plan participants when they purchase pharmaceuticals. Furthermore, to the extent that the overall health insurance market is competitive and health care costs are ultimately borne by employees, economists argue that the cost savings will also be reflected in lower premiums and higher wages to the plan participants (Pauly 1998). Because most privately insured employer-based plans integrate drug coverage with other forms of health care services, it is difficult, however, to isolate the distributional effects of generic savings.

## V. Generic Competition from an International Perspective

Danzon and Chao (2000) examined the effects of generic competition on pharmaceutical prices in countries with alternative regulatory regimes. In particular, to analyze this issue, they utilize comprehensive data on outpatient drug sales in 1992 for seven countries (Canada, France, Germany, Italy, Japan, the United Kingdom, and the United States). These countries were selected to provide a spectrum of price regulation and competition. In particular, the United States had virtually free pricing of prescription drug products. By contrast, France, Italy, and Japan were characterized by strong systems of price regulation on a product-by-product basis (as well as sharply declining trends in overall drug prices). The United Kingdom, Germany, and Canada were intermediate cases with considerable discretion to price new drug products, but they were also subject to either profit constraints (the United Kingdom), price caps adjusted for inflation (Canada), or a reference pricing reimbursement system (Germany).

A key finding was that the price sensitivity with respect to the number of generic competitors was greatest in the case of the United States (with a price elasticity of  $-0.50$ ).<sup>14</sup> Danzon and Chao also found that the United States had more generic entrants, more generic price competition, and higher returns to later entrants than in the more regulated price environments.<sup>15</sup> Germany, the United Kingdom, and Canada also exhibited significant price sensitivities to generic competitors. Germany, in particular, with its reference

price system had an effect on prices of generic competition that was most similar to that of the United States.

Little association was found between drug prices and the number of generic competitors in Japan, France, or Italy. Their price regulatory plans apparently undermined generic competition. In the case of France and Italy, products were typically introduced with prices well below those of other major pharmaceutical markets. There was also little possibility for inflation adjustments, so real product prices exhibited a down spiral over time. Consequently, firms have little incentive to introduce multisource drugs, and when they do, they are frequently new forms of old molecules to obtain a higher regulated price. Generic competition was also undermined in France and Italy by the regulation of retail pharmacy. Pharmacists were paid a regulated dispensing margin based on product price, and the requirement to dispense unit packs reduced the potential for volume discounts. In the case of Japan, physicians dispensed drugs directly and were strongly motivated to prescribe drugs with the highest margin between the reimbursed price and the acquisition price.

A relevant issue is whether the regulatory pressures on prices over the product life cycle in countries with stringent price regulation like Japan, France, and Italy achieve similar effects to generic competition in less regulated markets like the United States, the United Kingdom, or Germany. The net welfare effects are not comparable in the two contexts. First, the stringent price regulatory policies followed in countries such as Italy, France, and Japan have had a deleterious effect on drug innovation incentives in these countries (Grabowski and Wang 2006). Second, the lack of a competitive retail pharmacy system in France and Italy means that pharmacists and wholesalers capture part of the potential savings from lower prices in these countries (as do physicians in Japan from dispensing drugs with the highest margins).

One lesson from this multicountry study is that a reference-based price system of reimbursement can produce powerful incentives for generic competition and lower drug prices for a particular molecule. This is significant because several other countries such as Denmark, Norway, and the Netherlands have adopted reference pricing and have experienced rising levels of generic competition in recent periods. In the case of the United Kingdom, the incentives for generic usage have emanated from physicians. In particular, the British National Health Service (NHS) allows holding general practitioners who underspend their budgets to reinvest the savings in their practice. Baines, Tally, and Whyne (1997) found the main impact of the fund-holding program was to encourage more generic prescribing.

## VI. Effective Patent Life and Drug Innovation

In designing a patent system or set of intellectual property rights, the key policy challenge is setting the optimal balance between short-term benefits from greater price competition and longer-term benefits from greater incentives for innovation. This balance is particularly important in the case of an innovative industry like pharmaceuticals in which there are high social returns to innovation (see, e.g., Cutler and McClellan 2001a; Murphy and Topel 2003; Hsieh et al., Chapter 13).

Patents are considered critically important to research-oriented pharmaceutical firms in obtaining positive returns from innovations. This has been demonstrated in several economic studies.<sup>16</sup> In cross-industry analyses, Levin et al. (1987) and Cohen, Nelson, and Walsh (2002) found that the pharmaceutical industry placed the highest importance on patents. By contrast, many other research-intensive industries, such as computers and semiconductors, placed greater stress on factors like lead time and efficiencies in the production of new products accruing to first movers.

The critical importance of patents to research-intensive pharmaceutical firms follows directly from the characteristics of the drug innovation process. In essence, imitation costs in pharmaceuticals are extremely low compared to the innovators' costs of discovery and development. Pharmaceutical R&D is a complex, costly, risky, and time-consuming process. It has been estimated that the mean out-of-pocket R&D costs incurred by firms for a U.S. new drug approval is in excess of \$400 million (DiMasi, Hansen, and Grabowski 2003). By contrast, the cost of a generic firm to obtain an ANDA has been estimated to be only about \$1 million. Hence, absent patent protection or some equivalent barrier to entry, imitators could free ride on the innovators' FDA approval and duplicate the compound for a small fraction of the innovator's cost of discovering and developing a new drug.

Given the high costs of drug innovation relative to imitation, effective patent life (EPL), defined as the patent life remaining after a product is approved by the FDA, is an important factor in drug company decisions to undertake an R&D project. Companies typically file their key patent application prior to the start of clinical testing. Because of the long clinical trial period and regulatory review periods that occur in pharmaceuticals, much of the nominal patent life of 20 years is lost prior to FDA approval. At the time of the passage of the Hatch-Waxman Act in 1984, effective patent life for the representative new drug compound was less than 10 years and exhibited a declining trend (Grabowski and Vernon 2000).

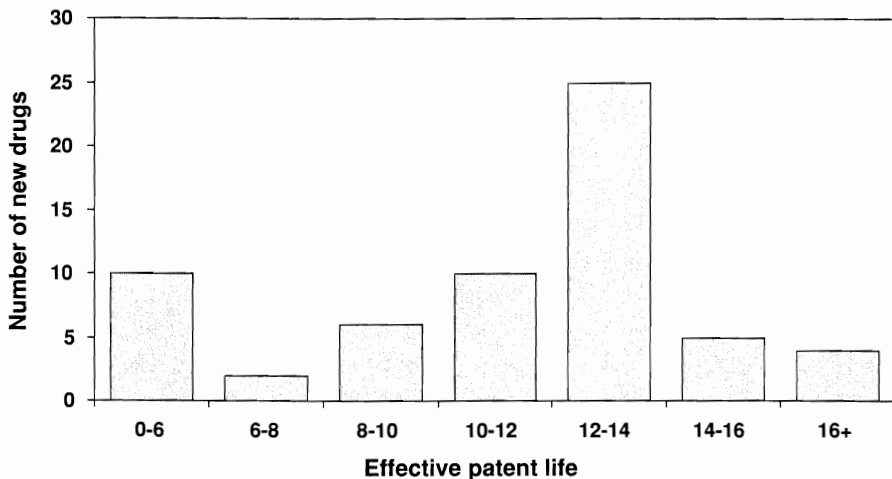


Figure 8.2. Frequency distribution of EPL 1993–1995 introductions.

In the Hatch-Waxman Act, Congress attempted to balance the incentives for innovative and imitative competition. Title II of the law provided for partial restoration of the patent time lost during the clinical and regulatory periods. In particular, new drugs were eligible for a Hatch-Waxman extension in patent life equal to the sum of the NDA regulatory review time plus one-half of the IND testing time. The law also constrained extensions to a maximum effective patent lifetime of 14 years and capped extensions at five years. In addition, Title I of the law involving ANDAs and generic competition provided for a five-year data exclusivity period. In essence, no generic firm could submit an ANDA and rely on the safety and efficacy data of the innovating firm until five years after FDA approval.

John Vernon and I (2000) examined the effect of Hatch-Waxman Act on effective patent life for 1990–1995 new chemical entities (NCEs). We found that the mean effective patent life was 11.7 years, with patent term extension contributing 2.3 years to this EPL. This EPL also included a 0.4-year average extension from the passage of GATT, which harmonized global IP rules. Subsequently, some of these NCEs also earned additional six-month exclusivity for doing further clinical trials to establish a pediatric dose under the Prescription Drug User Fee Act of 1994.

While the average effective patent life for new drugs was about 12 years, there was also considerable heterogeneity in the effective patent life across NCEs. Figure 8.2 shows the frequency distribution for the 62 NCEs approved over the last three years of our sample (1993–1995). The mode of the

distribution is the 12–14 year EPL interval. A little over 70% of the NCEs in the sample had EPLs in excess of 10 years. At the bottom of the spectrum, 15% of the NCEs in the sample were relying on the five-year data exclusivity as their main form of IP protection (Grabowski and Vernon 2000, p. 110). A new paper by Grabowski and Kyle (2006) found that actual market exclusivity times, defined as the period between brand launch and the entry of the first generic, exhibit a similar distribution. This analysis focused on the sample of new molecular entities that experienced their first generic entry between 1995 and 2005. One interesting finding is the large number of drugs with small market size (i.e., below \$100 million in the preentry period) that now have generic competitors. Generic firms appear to be broadening their portfolios to include even niche products with small sales in more recent time periods.

The U.S. Congressional Budget Office (1998) has conducted an analysis of the economic effects of the Act. As discussed in Section IV, they estimated the increased generic competition fostered by the Act has resulted in annual savings of \$8–10 billion to consumers by the mid-1990s. From the perspective of R&D returns, however, the CBO (1998, p. 38) estimated a negative effect in the after-tax profits to innovators. The framework the CBO utilized is illustrated in Figure 8.3.<sup>17</sup> Utilizing data from an analysis of R&D returns on pharmaceuticals in the 1980s combined with other information, the CBO estimated that the present value of cash flows from a representative new drug introduction declined by an average of 12% as a result of increased generic competition facilitated by the 1984 Act. In essence, the much more rapid loss of sales after generic entry (Fig. 8.3) has outweighed any patent term extensions provided by the Act. This can result in particularly adverse consequences for compounds of above-average riskiness, or those with shorter-than-average effective life.

Despite these negative estimated effects of the Act on innovative returns, pharmaceutical R&D has continued to grow at a substantial rate since the passage of the 1984 Act (Scherer 2001). Grabowski and Wang (2006) also have found an upward trend since 1983 in the number of high-quality or important drug introductions (as measured by the number of first-in-class and new drugs introduced in a majority of leading drug markets). This underscores the importance of examining both partial equilibrium effects as well as system-wide performance influences in considering the impact of new policy measures. This is especially important given the fact that the pharmaceutical industry now appears to have entered a more difficult period in terms of its R&D costs and returns and is experiencing generic challenges to innovators' patents much earlier in the product life cycle than

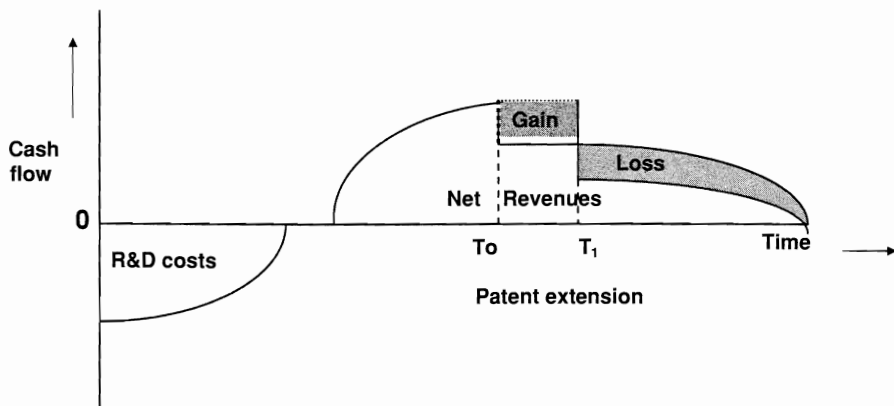


Figure 8.3. Conceptual framework for evaluating effects of the 1984 Act on R&D returns.

was previously the case (Grabowski 2004; Scherer 2001). Hence, effects of generic competition on drug innovation now may reinforce rather than counter other industry developments and be more pronounced in nature. This issue is considered in the next section of the paper, along with various policy options.

## VII. Strategic Responses of Brand and Generic Firms to the 1984 Act

### Life Cycle Management Strategies of Brand Firms

Given the large decline in expected sales that typically occur where generics enter the market, brand firms begin planning a strategic response to this entry well in advance of the patent expiration of a commercially important product. These responses are typically referred to as life cycle management strategies. Among the options available to brand firms are (1) the introduction of a new class of therapeutics for the same indication; (2) the introduction of a new formulation (e.g., a new delivery system or a combination product) that has improved therapeutic benefits in terms of patient tolerance, compliance, safety or efficacy; and (3) the introduction of an over-the-counter version of the product. Each of these strategies has been employed on a selective basis with some success by brand firms.

Arguably, the most effective life cycle management strategy is the introduction of a new class of therapies. Competition evolves in pharmaceuticals by the introduction of new classes of entities with superior therapeutic properties to prior generations of products. Firms that have a commercially



important product subject to patent expiration will frequently be conducting R&D on new therapeutic approaches for the same indication. However, there are no guarantees in this regard because the candidates for the next advance in therapeutics often span a large spectrum. Furthermore, the R&D process is subject to many technical, regulatory, and competitive uncertainties with long time durations.

Another life cycle management option for the brand firm is the introduction of a product line extension such as a new delivery system. Under the Hatch-Waxman Act, a new formulation involving additional clinical trials is eligible for a three-year exclusivity period. Moreover, a new delivery mechanism or formulation may be covered by a new patent. One of the most successful cases in this regard was the introduction by Pfizer of Procardia XL, a once-a-day formulation of a leading calcium channel blocker for hypertension. The extended release version of Procardia improved the tolerability and the side-effects profile associated with the active ingredient. As a consequence, Procardia XL turned out to be a much larger commercial success than the earlier formulation of Procardia. This life cycle management strategy has been employed in several other situations with somewhat mixed success. The weekly formulation of Prozac, for example, has enjoyed only very limited success. The degree of therapeutic improvement is a key factor in the success of this life cycle management strategy.<sup>18</sup>

A third basic option available in the case of some therapeutic categories is to develop an over-the-counter version of a product subject to patent expiration. The strategy has been employed for example for anti-inflammatory pain relievers such as Motrin and Naprosyn, anti-ulcer therapies such as the H<sub>2</sub> blockers Tagamet and Zantac, proton pump inhibitors such as Prilosec, and in several other therapeutic categories. However, a shift to OTC status requires approval by the FDA that the drug is safe for self-medication (Juhl 2000; McCarran 1991; Schweitzer 1997). A company will normally need to submit new clinical trial evidence to that effect. If approved by the FDA, the company receives a three-year exclusivity period for its OTC product in recognition for the new clinical trial work.

A key driver of success in the OTC market is the ability to capitalize on the brand loyalty enjoyed by the prescription product. The number of category shifts to OTC status approved by the FDA has grown over time. At the same time, there are many therapeutic categories where this is not as viable strategy because they would not meet the FDA's requirement on safety for self-medication (e.g., mental health and cancer drugs). The FDA has also declined several product requests for shifts to OTC status, such as anticholesterol drug agents.

### Patent Challenges and the Strategic Use of the Hatch-Waxman Act by Brand Firms

The Hatch-Waxman Act includes a marketing exclusivity provision that rewards generic firms for successfully challenging a patent in court on the basis of invalidity or noninfringement. To initiate the process, the generic firm files an ANDA with the FDA asserting the patent is invalid or noninfringed (a so-called Paragraph IV filing). The branded firm has 45 days to file an infringement suit. The law also provides for a stay of up to 30 months on approval of the ANDA while the patent infringement suit is ongoing. The first generic to file and prevail on a patent challenge obtains a 180-day marketing exclusivity.

Some practices utilized by brand firms to delay generic competition have been the target of recent FTC and legislative actions. One concern was the practice of listing several new patents late in the product life cycle in an apparent effort to trigger successive 30-month stays to delay generic competition. To prevent this practice, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 limited each branded product to one 30-month stay (Padden and Jenkins 2004).

The generic entrant with first-to-file exclusivity rights and the brand manufacturer has sometimes entered into an agreement whereby the generic firm receives compensation from the branded firm for not entering the market. Where there is uncertainty about the outcome of the patent case, this may be an attractive economic outcome to both parties. However, payers and consumers generally lose when price competition is delayed through such agreements. This practice has been subject to successful antitrust prosecution and class action suits, and is also further constrained under the Medicare Prescription Drug Act.<sup>19</sup>

### Patent Challenges and Strategic Uses of the 1984 Act by Generic Firms

While potential anticompetitive abuses of the 30-month stay have been addressed by recent litigation, the 180-day exclusivity provision for successful generic challenges remains in effect. In effect, this provision is an invitation to the generic firms to trigger a lawsuit. Even if the odds of winning are low, the payoff to successfully challenging a blockbuster patent is large. Since the 180-day exclusivity goes to the first firm filing and successfully challenging the patent, there is now a race to obtain exclusivity status of commercially significant projects. The FDA accepts a Paragraph IV ANDA

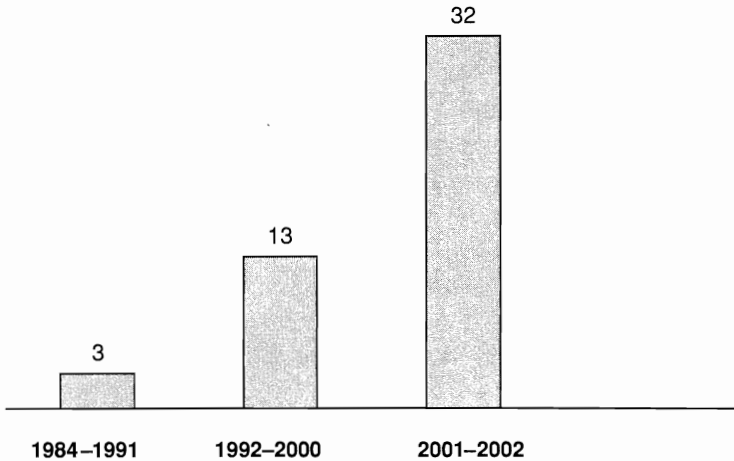


Figure 8.4. Average number of Paragraph IV ANDA filings per year. *Source:* U.S. Federal Trade Commission, Bear Stearns.

filing four years after approval of the pioneering product in recognition of the five-year data exclusivity. Generic marketing can begin as soon as the courts have resolved the suits or the 30-month stay has expired. This creates a range on exclusivity times of between five and seven and a half years.

Multiple lawsuits involving infringement have become the rule for the commercially important drugs early in the brand product's life cycle. The number of Paragraph IV ANDA filings has increased from three per year in the years 1984-1991 to 13 per year in 1992-2000 to 32 per year in 2001-2002 (Fig. 8.4). If a substantial fraction of these early-stage patent challenges are overturned by the courts, this would likely have significant adverse effects on the long-term expectations regarding R&D returns in this industry. As of June 2002, generic firms had won the vast majority of the suits, but most of these cases with outcomes to date involve late-stage patent challenges (Bear Stearns 2002; U.S. Federal Trade Commission 2002).

A patent can be challenged on the grounds of obviousness, prior art, or double patenting. A court may determine, for example, that a drug invention was "obvious," allowing the generic challenger to enter if the five-year data exclusivity period has expired. The issue of patent type is also relevant from a policy standpoint. Process, method-of-use, and formulation patents have less breadth than product patents and may be more vulnerable to challenge, although each situation must be evaluated on a case-by-case basis. It is worth noting that many important drug products such as the first AIDS therapy AZT (Zidovudine) relied on formulation or method-of-use patents because their product patents had already expired.<sup>20</sup>

From a strategic perspective, generic firms are prospecting in patent suits. They are spending millions of dollars in filing and litigation fees with their portfolio of patent challenges for the rights to obtain a very large payoff from the 180-day exclusivity period if they win a few of these suits. However, this wave of lawsuits crowds the courts and creates uncertainty around the commercial viability of the innovator's product. Furthermore, this uncertainty adversely affects market valuations of research-oriented pharmaceutical firms. It can cause firms to abandon R&D projects on future drug candidates with uncertain patent prospects. In addition, early patent challenges with uncertain outcomes can have a chilling effect on development of new indications and formulations. In particular, there may be no way to prevent cheaper generics from being used for the new indication after they enter the market even if they do not have an approved label for that indication.<sup>21</sup>

The five-year NCE data exclusivity was put into the Hatch-Waxman Act to incentivize innovators faced with little or no patent exclusivity time. However, this exclusivity period as currently constituted in the United States is not sufficient to sustain a high level of R&D activity. Since the 1984 Act was enacted, R&D costs have more than doubled in real terms (DiMasi, Hansen, and Grabowski 2003). At the same time, generic competition has become more intense. As discussed, generic patent challenges are occurring very early in the product life cycle. The NCE data exclusivity affords branded products a floor of effective exclusivity, depending on how long courts take to resolve in infringement suits. This is insufficient time for most new drugs to recoup the upfront R&D costs and earn a positive return on this investment.

In the European Union, new drugs receiving approval by the European Agency for the Evaluation of Medicinal Products (EMA) or by individual EU countries receive a 10-year data exclusivity period. In particular, generic firms can file an abridged market application after eight years from the date of first EU authorization and begin the process of development and license application. However, the license may not be effective until 10 years of exclusivity from licensing has expired. This is commonly called the "eight plus two" policy.<sup>22</sup>

This is a policy option that U.S. policy makers should consider as a means for preserving R&D incentives under the Hatch-Waxman Act. A 10-year NCE data exclusivity period recognizes the high R&D costs of drug innovation and operates to discourage patent challenges early in the product life cycle. This would defer early patent challenges because few imitators are likely to incur the high cost of a new drug application (i.e., repeating safety and efficacy trials, a process that also raises ethical issues) that would

be necessary to enter before the expiration of the 10-year data exclusivity period.

In terms of the objective of the 1984 Act to encourage innovation, a 10-year data exclusivity is more closely aligned with the minimum time necessary for the typical new chemical entity to earn a positive return on the large, upfront R&D investment now required for FDA approval (Grabowski and Vernon 2000). On these grounds, it would be a reasonable reform policy for policy makers to consider in the face of the explosion in patent challenges that has occurred in recent years. These challenges have led to higher litigation expenses and potential disincentives for R&D investments in new drugs and new indications for recently launched drugs.

### VIII. Summary and Conclusions

The 1984 Hatch-Waxman Act has maintained a reasonable balance between generic competition and innovation incentives. Under the patent restoration provisions of the Act, branded products typically enjoy an exclusivity period of 10–14 years. After patents expire and generic entry occurs, prices for the molecule typically decline markedly. Prices approach marginal costs when a large number of generics are present in the market. Generics now account for over 50% of U.S. prescriptions; thus the savings to the payers and consumers of drug products have been substantial (U.S. Congressional Budget Office 1998).

Both brand and generic firms have responded to the law with strategies designed to create competitive advantages. Brand firms have utilized a variety of life cycle management strategies. These include new product formulations, shifts of the brand to OTC status, and authorized generics. These strategies are all legal and generally procompetitive, although they are limited in applicability to particular situations and therapeutic classes. At the same time, the U.S. Congress has recently acted to prohibit some life cycle management strategies that are not typically procompetitive such as agreements between generics and branded firms or the use of multiple 30-month stays to deter entry.

One aspect of the law that needs further scrutiny by policy makers is the 180-day exclusivity period that is awarded to the first generic firm that successfully challenges a patent. As generic competition has intensified, the strategic advantage to generic firms of the 180-day exclusivity period has become more valuable. Accordingly, they are devoting increasing resources to gaining core competencies in the art of patent challenges. This has led to a race to litigate as generics file challenges to the patents of commercially

important products as soon as legally possible. Left unchecked, this wave of litigation early in the product life cycle could upset the delicate balance between price competition and innovation that has existed in the two decades since the 1984 Act was passed.

Another issue that warrants policy consideration is the question of generic or follow-on biologicals. New biological entities are regulated by a different division of the FDA. Follow-on biologicals are not covered by the Hatch-Waxman Act. A few of the older biologicals, such as human growth hormone, have multiple suppliers, but they are branded products that have performed additional safety and efficacy trials to gain FDA approval. The process for developing and manufacturing a new biological is more complex than in the case of new chemical entities. There are scientific, regulatory, and economic issues that need to be examined in the case of follow-on biologicals (Grabowski, Cockburn, and Long 2006). Congress and the FDA are currently considering whether regulatory procedures for follow-on biologicals should be changed. Given that a number of commercially important biologicals are scheduled to experience patent expiration in the next five years, this will also continue to be an important issue for further research and attention by policy makers.

Outside the United States, generic competition has had a significant effect on prices in countries that encourage generics through reference pricing-based reimbursement systems (e.g., Germany) as well as countries that create significant incentive programs for physicians to prescribe generically (the United Kingdom). By contrast, countries like France and Italy, which have stringent price regulation of new product launches and declining prices over time, along with competitive barriers in their pharmacy distribution system, have experienced negligible benefits or savings from generic competition.

## Chapter 8. Competition between Generic and Branded Drugs

1. One notable exception to this situation involved antibiotic drugs. These drugs did not have to conduct any new safety and efficacy trials because FDA approval of generic antibiotics was governed by the reference monograph approach. Specifically, generic antibiotic products had to show only therapeutic equivalence to the corresponding branded entity.
2. H.R. 98–857 (I) at 16 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2649.
3. Preface to the 22nd edition of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the "Orange Book."
4. Orange Book, preface.
5. This list is also available on line at [www.express-scripts.com/ourcompany/pressroom/mediakit/generics/docs/laws.pdf](http://www.express-scripts.com/ourcompany/pressroom/mediakit/generics/docs/laws.pdf), accessed June 27, 2006.
6. PhRMA (2000), p. 66, based on original data from IMS® Health 2000.
7. Capitation is a method of payment in which a physician receives a fixed amount for each person eligible to receive services (dollar/participant/month).
8. See, e.g., Grabowski and Vernon (1996), Masson and Steiner (1985), and Bloom, Wiertz, and Pauly (1986).
9. Ironically, this can lead to the government's paying a higher price for the generic product compared to its branded version when generics first enter the market. This can occur because brand manufacturers are required to give Medicaid discounts based on their "best price" to any buyer and, in any case, a minimum discount of 15.1%. The comparable requirement for generics is 11%. For example, the state of Maine, in 2001, initially paid 17% more for the generic fluoxetine than it had been paying for Prozac prior to automatically switching Medicaid users to the generic (Caffrey 2002).
10. Data audits of IMS Health as reported in PhRMA 2000 *Pharmaceutical Industry Profile* and subsequent IMS news releases.
11. For a simultaneous equation analysis of these various market variables, see Saha et al. (2006).
12. Richard Frank and David Salkever (1992, 1997) find the impact was positive, consistent with specific conditions on a brand firm's demand curve becoming more inelastic after generic entry. More recently, Saha et al. (2006), focusing on the 1990s, found that the net impact of generics on the rate of change in prices was negative, but relatively small in magnitude. In particular, they found that it takes 16 or more generic entrants to cause brand prices to actually decline in value in the first full year after generic entry.
13. One key assumption is that total sales of the molecule remain constant in terms of units in the face of generic competition (zero elasticity of demand). This can lead to an overstatement of savings, but studies of the effect of generic competition

on the sales of the molecule indicate this is a reasonable first approximation (IMS generic spectra product summaries in 2002).

14. The sample involves a regression analysis framework that estimates the effect on price of the number of generic products of the same molecules. Danzon and Chao (2000) also control for the number of therapeutic substitutes, first-mover advantages, molecule age, and several other factors.
15. In a related approach involving a multicountry study, Hudson (2000) found that the impact on brand sales from generic entry is much greater in the case of the United States compared to the United Kingdom, Germany, or France.
16. For example, Edwin Mansfield (1986) surveyed the chief research officers of 100 U.S. corporations and found that 60% of the innovations commercialized in 1981–1983 by the pharmaceutical firms would not have been developed without patent protection. The mean for all industry was 14%.
17. This framework was originally employed by Grabowski and Vernon (1986) to simulate the potential effects of the Act on R&D returns when the Act was first passed.
18. Another formulation strategy for the life cycle management is to combine a drug product subject to patent expiration with a newer product that has a much longer effective patent. In this case one needs to demonstrate to the FDA that the product, in combination, has a synergistic effect. According to IMS (2004), fixed combinations have become an important life cycle management approach in recent years.
19. Any agreements among ANDA applicants and brand name companies, or involving other ANDA applicants, must be filed with the Federal Trade Commission and the Department of Justice within 10 days of execution (Padden and Jenkins 2004).
20. AZT was originally developed unsuccessfully as a cancer remedy and remained as an unapproved drug candidate until its antiviral activity was discovered in the mid-1980s. For a case history, see Emmons and Nimgade (1991).
21. When a new indication is approved, only that indication receives three years of additional exclusivity under the Act. However, there is no effective way to prevent a less expensive generic firm from being used for all indications during this three-year exclusivity period, since physicians do not specify an indication when they write a prescription. This will be the case unless the brand firm utilizes an alternative delivery system or formulation that has exclusivity or patent protection.
22. In addition the EU law also allows for one year of additional data exclusivity for the whole compound if additional indications of significant overall therapeutic value are approved within the eight-year period (Towse 2004).