Pharmaceutical Lifecycle Extension Strategies

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Abstract

The combination of higher drug costs of drug development and an increasing share of generics has lead pharmaceutical firms to focus on alternative strategies to make profits. An important development in the pharmaceutical industry is the focus on strategies that increase the returns from an already approved drug, before and after its patent has expired. These lifecycle extension strategies can be divided into marketing strategies (pricing, promotion, divestiture, differentiation, over-the-counter drugs, and branded generics), R&D strategies (new indications, reformulations, combination drugs, and next-generation drugs), and legal strategies (generic settlements and patenting). For example, when the patent of the blockbuster drug Prilosec was about to expire in 2001, its manufacturer was pursuing many different lifecycle extension strategies concurrently. Already 6 years before patent expiry its legal, marketing, and R&D experts had started with the development of over 50 different strategies to soften the impact of the patent expiry, such as a next-generation product, introducing branded generics, and improving the patent protection of the product. This chapter provides a comprehensive framework to classify the various lifecycle extension strategies, gives an in-depth overview of the research on the different strategies, and identifies gaps in our knowledge on these strategies to guide future research.
Introduction

The pharmaceutical industry is heavily spending on developing new prescription drugs, which are protected by patents to enable firms to recoup their research and development (R&D) costs. When the patent on a branded drug expires, generic drugs enter the market to compete based on price. Dimasi, Hansen and Grabowski (2003) estimate the development costs of an average drug at $802 million in 2000. While the costs of new drug development have risen enormously over the last 60 years, the number of newly approved drugs has remained relatively stable (see Figure 1; Cockburn 2007; Munos 2009). In 2008, the pharmaceutical industry spent $50 billion on R&D and 21 new drugs have been approved in the United States (Munos 2009).

At the same time, the share of generic drugs has increased substantially. The generic share of prescription drugs in the United States has risen from 18.6% of unit sales in 1984 to 78% in 2010 (Forden 2011; Frank 2007b). The current generic share is comparable for most other countries with high drug sales, although in some countries like France, Italy, Japan, and United Kingdom the generic share is 50-60% (Danzon and Furukawa 2008). The rise of the generic share has several reasons. The growth of managed care organizations (MCO) and health maintenance organizations (HMOs) have increased the emphasis on generics. Pharmacy benefit managers (PBMs) act as managers for reimbursement for firms and HMOs and stimulate the usage of generic drugs. In several countries – such as the United States, Canada, and Belgium – insurers have introduced tiered copayments (or partial reimbursement rates) and generics have the lowest copayments. Pharmacists have been incentivized to prescribe more generics, due to higher margins (Grabowski and Vernon 1992). Many countries and all states in the United States have now laws in place that permit pharmacists or make it compulsory for them to substitute a branded drug by a generic if one is available.
(Vivian 2008). Hellerstein (1998) reports that, in 1995, pharmacists already substituted generics in half of the cases when the doctor prescribed a branded drug. An extensive literature has discussed the determinants (e.g. Grabowski and Kyle 2007; Grabowski and Vernon 1992; Hurwitz and Caves 1988; Saha et al. 2006; Scott Morton 2000) and consequences of generic entry (e.g. Caves, Whinston and Hurwitz 1991; Hurwitz and Caves 1988; Reiffen and Ward 2005; Saha et al. 2006). This literature shows that the number of generic entrants decreases the generic price. The number of generic entrants is mainly driven by market size, pre-patent expiry advertising, and the ease of manufacturing. The generic share increases in the extent of HMO coverage and is larger in hospital markets. In addition, most studies find that generic entry decreases the total market size of the molecule, branded prices increase after generic entry, and marketing expenditures decrease before and after patent expiry.

The combination of higher costs of drug development and an increasing share of generics has lead firms to focus on alternative strategies to make profits. An important development in the industry is the focus on strategies that increase the returns from an already approved drug. Firms have various possibilities to extend the lifecycle and profitability of a branded drug, before and after its patent has expired. These lifecycle extension strategies can be divided into marketing strategies, R&D strategies, and legal strategies (see Figure 2)\(^1\). In this chapter, I discuss these pharmaceutical lifecycle extension strategies and focus on providing an overview of prior academic research and directions for future research\(^2\).

\[\text{[Insert Figure 2 about here]}\]

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1 Another consequence of the increasing market share of generics is that many branded manufacturers have recently moved into the generics industry via acquisitions.

2 There are plenty of cases written about specific lifecycle extension strategies. For example, Kvesic (2009) discusses various lifecycle extensions of nifedipine (Adalat, Procardia) over a 30-year period, such as new indications, new dosages, a combination drug, etc. Chandon (2004) is another excellent case, discussing the strategies used by Clamoxy in France to fend off generics.
Marketing strategies to extend the lifecycle of a branded drug include the pricing of the drug before and after patent expiry, the promotion strategy, differentiation strategies, the divestment of a drug, the introduction of branded generics, and making the drug available over-the-counter (OTC). Marketing strategies can be executed relatively quickly compared to other lifecycle extension strategies. The price of the branded drug before and after patent expiry is important as generics enter the market with substantially lower prices and margins than the branded drug (Frank and Salkever 1997; Grabowski and Vernon 1992). When the number of generics increases, the generic prices approach marginal costs (Reiffen and Ward 2005). The branded manufacturer may decide to decrease its price to face head-to-head competition with generics, or maintain or even increase its price to focus on the price-insensitive segment of the market and benefit from its brand equity (Frank and Salkever 1992). At the same time, the firm has to decide on the promotion for the branded drug around patent expiry (Berndt, Kyle and Ling 2003). The branded drug has enjoyed a legal monopoly during its patent-protection period and likely has built substantial brand equity and goodwill (Caves, Whinston and Hurwitz 1991; Hurwitz and Caves 1988). Around patent expiration, the firm must decide on whether to keep investing in this brand equity, focus the promotion on specific segments of the market, or largely cut the promotion. The marketing department of the firm can also decide to differentiate the branded drugs from generics by providing additional value to its product, without obtaining a new patent (Chandon 2004; Kvesic 2008). For example, they can offer extra service to their product or produce a different flavor of the drug. Furthermore, firms can decide to divest or milk their product (Kvesic 2008).

The introduction of branded generics and switching a drug to become available OTC require a long-term commitment of a firm and may bring a healthy stream of revenues over a longer period of time. Branded generics are cheaper versions of the branded drug that build on the branded drug’s name and are marketed or licensed by the manufacturer (Berndt et al.
This allows the firm to capture a share of the generic profits and possibly increase the equilibrium price of generics, which in turn may lead to a higher share for the branded drug (Kamien and Zang 1999; Reiffen and Ward 2007). A firm can also opt to make the drug available to consumers by getting OTC approval (Berndt, Kyle and Ling 2003; Ling, Berndt and Kyle 2002). This option is limited to drugs that have a low potential for abuse and have proven to be reasonably safe and well tolerated. OTC drugs make up 28% of the unit prescriptions in the United States (Danzon and Furukawa 2008).

R&D strategies require more time to execute, but potentially have a long-term impact on the sales of the drug. The advantage of R&D into extensions of an existing drug is that it can benefit from the information obtained from past clinical trials (O’Connor and Roth 2005). This makes drug development more efficient and decreases the development costs and risks substantially (Chong and Sullivan 2007; Fleming and Ma 2002). New indications and reformulations are frequently used R&D strategies to extend a drug’s lifecycle (Dubey and Dubey 2009). Upon approval, both can extend the monopoly period of the branded drug for several years. Increasing the number of approved indications also expands the potential market for the drug. In 2004, 84% of the top 50 prescription drugs had obtained additional indications after approval (Sandner and Ziegelbauer 2008). Reformulations use the same active ingredient as the original drug, but provide substantial improvements to the drug that make the drug more effective, reduce side effects, or provide patients with more convenience. Between 1989 and 2000, 65% of the approved drugs in the United States were reformulated versions of existing drugs (Hong et al. 2005). Firms can also opt for combination drugs, which are two or more drugs (i.e. pills, injections, patches, or inhalers) combined into one drug (i.e. pill, injection, patch, or inhaler) (Herrick and Million 2007). In 2009, worldwide sales for combination drug were over $30 billion. Combination drugs require more substantial R&D investments, but can receive their own patent. Similarly, firms can develop a
next-generation product that is based on a drug already on the market, but qualifies for a new patent as it consists of a new molecule (e.g. Nexium is the next-generation product of Prilosec).

Legal strategies are also widely used to extend the lifecycle of a drug and have a short to medium-term impact on the sales of the drug (Burdon and Sloper 2003). As the branded drug’s lifecycle is mainly determined by the period without generic competition, firms use various legal strategies to deter generic entry. These comprise patenting strategies, where firms heavily protect their drug with multiple patents, and settling with generic manufacturers to postpone generic entry. For example, the average number of patents on a drug has seen a five-fold increase from 1995 to 2005 (Frank 2007b).³

The overall strategy of a branded firm around patent expiry often combines multiple strategies discussed above. These are not independent from each other and to decide on and execute these strategies knowledge from different departments in the company is needed, requiring the formation of cross-functional teams. For example, the development of a reformulation of a drug requires R&D input, a marketing plan, and support from the legal department on patenting and trademarking. Some lifecycle strategies require many years to develop (e.g. combination drugs due to new clinical trials), while others can be implemented overnight (e.g. price change). An active lifecycle strategy can start already before the launch of a new drug (e.g. see Figure 2 in Kvesic (2009) for various extensions of nifedipine).

A manufacturer has invested heavily in successful drugs that near patent expiry. In 2008, $50 billion was spent on R&D, not only to get drugs approved to the market, but also to continuously support drugs that are on the market. In addition, substantial amounts are spent on marketing drugs by informing and educating doctors, patients, etc. When the patent on a drug expires, the drug has built various assets that can be leveraged to extend a lifecycle.

³ Another strategy sometimes used by firms is to corner supply, whereby the manufacturer makes an exclusive contract with suppliers of scarce ingredients, prohibiting competitors to produce generics. I will not further discuss this strategy as it is questionable from a legal perspective.
To decide which lifecycle extension strategy a firm should pursue for a particular drug, a firm should evaluate its own assets and the assets of the drug. These can be divided into reputational assets and knowledge assets (Teece, Pisano and Shuen 1997). Reputational assets come from the brand and the company’s name. After patent expiry, the branded drug can benefit from its brand equity and trademarks. These give a quality signal to doctors and patients and lower informational costs (Landes and Posner 1987). This can be used to slow down the impact of generics and can be used for line extensions to leverage market power and brand equity from one market or product to another. The firm also has knowledge assets. Some of them are protected by patents, but most are due to the firm’s extensive experience in the market and in the development of the drug. These knowledge assets comprise expertise in technical areas, manufacturing, marketing, knowledge of doctor and patients, and a good network. These knowledge assets should also be carefully evaluated and used to decide on alternative lifecycle extension strategies. For example, this knowledge may help to identify new potential market applications for the branded drug.

In this chapter I focus on strategies that build on a drug that is already on the market and do not cover various related topics. These include a discussion of the general R&D process (e.g. Gauza, Llobet and Domínguez 2009) and the budgets set for R&D (e.g. Weiss, Naik and Weiss 2009). In addition, I refrain from discussing the technical aspect of the R&D process and an in-depth discussion of legal strategies. However, I will discuss the R&D and legal strategies at a more general level, as they are important strategies in themselves and because they are also closely related with the other lifecycle extension strategies.

Patent expiration has consequences for many different market players: Branded manufacturers, generic manufacturers, doctors, patients, insurers, pharmacists, and the government. I focus mainly on the consequences of patent expiry for branded manufacturers and will not extensively discuss the impact for the other players.
Finally, I limit the main discussion to pharmaceutical drugs and not discuss strategies for biologics. Biologics are still relatively new and regulations concerning generic biologics (also called biosimilars) are in flux (Engelberg, Kesselheim and Avorn 2009; Frank 2007a; Kozlowski et al. 2011). The end of this chapter will briefly discuss implications for biologics.

I continue by discussing the regulatory environment for prescription drugs, which is essential to understand the rest of the chapter. Then, I discuss the determinants and impact of generic entry. Next, I discuss the various lifecycle extension strategies in more detail and give specific recommendations for future research on them and I end with a conclusion and some more general recommendations for future research.

**Regulatory Environment**

New drugs are often protected by multiple patents. Patents allow firms to extract monopoly rents from their product for a limited period of time, often in return for high R&D investments. The total time a drug is on the market without facing generic competition is referred to as the market exclusivity period (e.g. Grabowski and Kyle 2007). Upon approval of a drug in the United States, its patents are listed in the Orange Book of the Food and Drug Administration (FDA)\(^4\). The most important patent on a drug protects the molecule. Internationally, the norm is that a patent lasts for 20 years from the date of application. However, after patenting firms need to test and prove the safety and efficacy of the drug to receive market approval from the national regulatory bodies. Both patents and drug approval by the regulatory body are needed to sell drug without liability (Bhat 2005)\(^5\). The time between patent filing and market approval can be substantial and shortens the patent-

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\(^5\) The market approval of a drug is regulated by the regulatory body of a country. In the United States this is the Food and Drug Administration (FDA), in Europe the European Medicines Agency (EMA), and in Japan the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). These agencies control the three largest pharmaceutical markets.
protected time of the branded drug on the market. Regulatory bodies often compensate for the lost time, as a result of clinical testing, by extending the patent or the market exclusivity period. In Europe, for example, a supplementary protection certificate (SPC) can be obtained extending the patent for a maximum of 5.5 years (Table 1 provides an overview of pharmaceutical terminology and abbreviations used in this chapter).

I discuss the US regulations in more detail. In 1984, US congress passed the Hatch-Waxman Act – also known as the Drug Price Competition and Patent Term Restoration Act – which regulates the competition between branded and generic drugs. It marks an important change in the US pharmaceutical market and applies to all pharmaceuticals, except antibiotics, and biotechnology products. I discuss two important parts of the Act.

Title I allows generic drug makers to file an abbreviated new drug application (ANDA), which involves a bioequivalent of a branded drug whose patent expires. Compared to before the Act, generic drug makers do not have to prove the safety and efficacy of the drug anymore, which involves substantial costs and creates high barriers to entry. The Act required generic manufacturers to only show bioequivalence of their drug.

Bioequivalence is typically shown by measuring and comparing the absorption of the branded and generic drug in the blood stream in around 30 healthy volunteers (Bhat 2005; Dubey and Dubey 2009). Testing for bioequivalence is 18 times cheaper than also repeating the safety and efficacy tests (Bae 1997). The costs to prepare an ANDA are about $1 million (Hemphill and Sampat 2011). The first generic manufacturer that successfully files an ANDA is granted an exclusive marketing period of 180 days for the drug among generic manufacturers. The Act also allows firms to test the patented drug before patent expiry and specifies a process to resolve a patent dispute between a branded and generic manufacturer.

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6 See for the complete law: Public Law 98-417.
An ANDA must contain one of the four certifications with respect to each patent listed for the branded drug. A ‘Paragraph I, II, and III Certification involve the assurance that respectively: (i) no patent for the branded drug is filed, (ii) the patent on the branded drug has expired, (iii) the approval of the ANDA is only sought after the patent on the branded drug has expired. A Paragraph IV Certification involves a claim of a generic manufacturer that the patent on the branded drug is invalid or will not be infringed (Bulow 2004; Hemphill and Sampat 2011). After an ANDA is filed by a generic manufacturer, based on a noninfringement claim, branded manufacturers can file a patent-infringement suit within 45 days. The FDA cannot approve the ANDA until a court invalidates the infringement or 30 months elapse (Bhat 2005). In 2003, the Medicare Prescription Drug, Improvement and Modernization Act (MMA) passed the senate to prevent branded manufacturers to exploit former law to delay generic entry. For example, firms started multiple patent-infringement litigations, which all provided a 30-month stay of generic drug approval. The new Act allows a maximum of one such extension. Higgins and Graham (2009) report that, between 1992 and 2000, branded firms started an infringement suit to 72% of the Paragraph IV challenges and the branded drug manufacturer won these litigations in 58% of the cases. They also report that the number of paragraph IV challenges has increased substantially after 2000.

Title II of the Hatch-Waxman Act grants additional market exclusivity to branded drugs for the time lost due to FDA drug review. On average, the additional market exclusivity granted is 2.5 to 3 years with a maximum of 5 additional years or 14 years from the original FDA approval date. Newly approved drugs get a minimum of 5 years market exclusivity. Firms need to apply for the extension within 60 days of market approval.

In all US states and many other countries there are generic substitution laws for pharmacists, allowing them or making it compulsory to substitute the branded prescription by a bioequivalent generic (Vivian 2008). This leads to a higher generic share. In some states
patients first need to give their consent prior to the generic substitution by the pharmacist, leading to a lower substitution rate (Shrank et al. 2010).

**Generic Entry**

When the patent on a drug expires, generic drugs can enter the market. These generics have substantially lower prices than the branded drug before patent expiry and take a large share of the market. Hellerstein (1998) finds that almost all doctors prescribe both generic and branded versions of the same molecule if a generic is available. They report substantial heterogeneity across doctors in the frequency of branded versus generic prescriptions.

The impact of patent expiry in the pharmaceutical industry is widely investigated. Regulations play an important role in the outcomes of patent expiry and in the United States the Hatch-Waxman Act in 1984 has changed the dynamics after patent expiry substantially. See for a comprehensive study on patent expiry before the Hatch-Waxman Act (Statman and Tyebjee 1981). Below, I focus mainly on patent expiry and generic entry after the Hatch-Waxman Act. Table 2 gives an overview of the empirical studies into patent expiry. I start by describing the characteristics of generic entry, followed by the consequences of generic entry.

[Insert Table 2 about here]

**Determinants of generic entry**

The time until generic entry is uncertain, because the approval time of an ANDA is uncertain. Branded manufacturers also do not know the exact patent expiry date, as patents can be challenged before the original patent expiry date. Generics entering the market are often considered a commodity, with little differentiation between them. Hence, the number of generic entrants largely determines their price, with more entrants implying a lower price.
The extent and speed of generic entry after patent expiry differ across products and markets. Scott Morton (2000) finds that the most important factor determining the number of generic entrants is the revenue of the branded drug before patent expiry (see also Grabowski and Vernon 1992; Hurwitz and Caves 1988; Saha et al. 2006). Sometimes a drug is in a niche category and no generic enters, e.g. between 1987 and 1993, 40% of the drugs faced no generic competition within two years after patent expiry (Bae 1997). Hurwitz and Caves (1988) also find that branded drugs with a longer market exclusivity period and higher pre-patent expiry promotional expenditures face fewer generic entrants.

Hudson (2000) investigates the impact of generic entry in four different countries: United States, United Kingdom, Germany, and Japan. He largely confirms the findings of earlier studies based on US data and finds that larger markets face more generic entrants and faster generic entry.

Grabowski and Kyle (2007) find in a recent large-scale study, based on 251 drugs that lost their patent between 1995 and 2005, that drugs face generic entry more often over time and that more successful drugs face more generic entrants and a smaller market exclusivity period.

**Consequences of generic entry**

Generic entry has a large impact on the market. It leads to drastic changes in the average price of a molecule as cheap generics enter and the demand for the branded drug largely shifts to generics. Below, I discuss the consequences of generic entry and also discuss how it influences the promotional expenditures and total market size.

Hurwitz and Caves (1988) investigate the impact of generic entry on the market share of the branded drug. They find for a sample of 29 drugs, expiring between 1978 and 1983 (before the Hatch-Waxman Act), that the share of the branded drug after generic entry is
proportional to the time of that drug on the market (goodwill stock) and its promotion. The goodwill and promotion are less effective for hospital markets than pharmacy markets.

Caves, Whinston and Hurwitz (1991) provide a descriptive analysis of the impact of generic entry in the United States for 30 drugs. They investigate the speed and fullness with which generic entry erodes the sales of the branded drug losing its patent. They analyze the period 1976-1987 and hence most patents in their sample expired before the Waxman-Hatch Act. They find a small decrease of the branded drug’s price as the number of generic entrants increases. The price of generics decreases with the number of generic competitors. The total generic share increases with the number of generic drugs available, but remains relatively small. They find that when the generic price is about half of the branded price, generics attain a 25% market share five years after patent expiry.

Grabowski and Vernon (1992) analyze prices and market shares of 18 high-sales drugs facing their first generic competition between 1984 and 1987, after the Waxman-Hatch Act. They find that overall market prices decline sharply in the first two years after patent expiry. During that period branded prices increase by 11% (see also Berndt, Kyle and Ling 2003), exceeding inflation. Generic prices are substantially lower and keep decreasing with additional generic entrants. Two years after patent expiry, the average generic share is 49%.

Wiggins and Maness (2004) find that generic and branded prices decrease in the number of entrants. They test this for a single therapeutic category (anti-infectives) and argue that this focus allows them to control for cost and demand differences across therapeutic categories. However, their results may partly be driven by the characteristics of the therapeutic class under consideration.

Reiffen and Ward (2005) investigate generic prices in reaction to generic entry using a structural model. Based on 31 drugs facing generic entry, they find that the number of generic entrants and the speed of generic entry increases with market size. They report that
the price for the first generic is 20-30% above long-term marginal costs, but generic prices begin to approach marginal costs when ten or more generic competitors have entered.

Saha et al. (2006) empirically investigate for 40 drugs the interactions among generic entry, prices, and market shares. They claim to be the first to analyze these three variables using a simultaneous estimation procedure to address the endogeneity between them. The price and share of generics are simultaneously determined. The number of generic entrants is a key determinant of generic market share and the generic-to-brand price ratio. They also find that the extent of HMO coverage increases generic market share.

Another reason for the decreasing market share of the branded drug is that its promotional expenditures decrease substantially around patent expiry (Caves, Whinston and Hurwitz 1991). Berndt, Kyle and Ling (2003) investigate the marketing expenditures of branded drugs around patent expiry. They find for four H$_2$-antagonist drugs that marketing expenditures between 24 and 1 months before patent expiration are 20-59% lower than the amount spent between 48 and 25 months before patent expiry. The amount spent on marketing in the first two years after patent expiry is even lower. This decrease in marketing expenditures is confirmed by Huskamp et al. (2008) and Iizuka (2004).

The market size can also change due to generic entry. Gonzalez et al. (2008) investigate how doctors change their prescription behavior in a therapeutic category when one of molecules (a branded drug) goes off patent. Due to the introduction of generics, the average price of the molecule that loses its patent decreases. In line with Caves, Whinston and Hurwitz (1991) they find that, despite the lower price for the molecule, total prescriptions decrease as some doctors switch to other branded and more expensive molecules.

The literature on generic entry has mainly investigated the US market as it is the biggest and least regulated pharmaceutical market in the world. However, these results are not directly generalizable to other countries due to differences in the regulatory context. For
example, many European countries have reference price systems, prohibiting branded drugs to increase prices after patent expiry. Hudson (2000) studies the impact of generic entry on sales in multiple countries. He confirms several results of earlier studies on US data and finds that, except for the United Kingdom, market size and the price of the branded drug increase the speed with which the branded drug loses its market share. In addition, he finds that the impact of generics is greater in the United States than in Germany, United Kingdom, and Japan. This can either be due to the US regulations or because the United States has the biggest market size among these countries. Lexchin (2004) analyzes price changes of branded drugs after patent expiry in Canada and finds no significant changes. Arronson, Bergman and Rudholm (2001) find for the Swedish pharmaceutical market that lower generic prices substantially decrease branded market share.

**Summary of generic entry**

The impact of generic entry on branded sales has substantially increased in the United States after the passage of the 1984 Hatch-Waxman Act. As generic drugs are a commodity, the main determinant of their impact is the number of generic entrants, which in turn decreases the generic price. This is mainly driven by market size, but pre-patent expiry advertising and the ease of manufacturing also influence the number of generic entrants. The generic share increases in the extent of HMO coverage and is larger in hospital markets. Generic entry decreases overall market size for that molecule due to a substantial decrease in marketing.

Hence, the number of entrants largely determines the generic price, but the literature is not converged on the effect of generic entry on branded prices. While most studies find that branded prices increase (e.g. Berndt, Kyle and Ling 2003; Grabowski and Vernon 1992; Regan 2008), some studies find decreasing prices after generic entry (e.g. Caves, Whinston and Hurwitz 1991; Wiggins and Maness 2004). These differences warrant a large-scale study.
analyzing price changes of branded drugs after patent expiry. It is valuable to explore the product and market moderators that explain the changes in branded prices after patent expiry.

The literature is consistent on firms decreasing their marketing expenditures before and after their patent expires (Berndt, Kyle and Ling 2003; Caves, Whinston and Hurwitz 1991). The literature is also consistent on a decreasing market size for the molecule after patent expiration (Caves, Whinston and Hurwitz 1991; Gonzalez et al. 2008), though this may not hold for current markets due to the advent of stronger managed care pressures.

**Marketing Strategies**

Firms of branded drugs that face patent expiration have different marketing tools to retain sales and soften the impact of generic entry. They can make their product attractive by the price, promotion, and by differentiating it from generics, to either limit the generic share directly or by deterring generic entry (Scott Morton 2000). A firm can also decide to divest its drug around patent expiry. In addition, the firm can introduce a branded generic or an OTC version of the drug. I discuss these marketing-related strategies in turn below.

**Pricing**

When the market exclusivity period for a drug ends, lower-priced generics enter the market. The branded drug manufacturer can react by decreasing the price to compete directly with the generics (e.g. Chandon 2004). For example, they can decrease the unit price or give volume discounts to large distributors or pharmacies. They can also maintain or increase the price and focus on the price-insensitive segment of the market, although price increases are not an option in countries where the price is regulated (e.g. Europe). In the United States the most common reaction of branded firms to generic entry is a price increase.
Frank and Salkever (1992) explain the price increase of branded drugs in response to generic entry by dividing the market into two segments. They show theoretically that a price increase after generic entry can be explained by optimal firm behavior. They distinguish a segment that is price insensitive (or brand loyal) to the branded drug and a price-sensitive segment. The price-insensitive segment can consist of patients of doctors in fee-for-service practices, while the price-sensitive segment consists of hospitals, HMOs and Medicaid patients. They conclude that generic entry decreases the price elasticity of the demand for the branded drug and hence a price increase for the branded drug is optimal (this is extended and confirmed by Regan (2008), who incorporates the payment type of the patient for the drug).

In a later paper Frank and Salkever (1997) confirm these predictions empirically. Gonzalez et al. (2008) use doctor-level data from the United Kingdom to study the patent expiry of Prozac. They confirm the existence of two doctor segments: a marketing-sensitive segment that prescribes less of the molecule losing its patent and switches to the more heavily marketed alternatives, and a smaller price-sensitive segment that starts prescribing the cheaper generics.

Hong et al. (2005) find that the price rigidity of branded drugs after patent expiry is due to the introduction of line extensions of the branded drug. As line extensions are closely related to the branded drug that loses its patent, the manufacturer sustains the price of the branded drug to increase the demand for its extension. This is in line with Kadiyali, Vïlcassim and Chintagunta (1996), who find that line extensions decrease the original product’s cross-price elasticity to competitors.

Ching (2010) finds evidence that myopic firms would set their price after patent expiry higher than long-term oriented firms, who take the learning about generic quality into account. A lower price for branded drugs decreases learning about the quality of generics.
Promotion

Manufacturers use the period in which the branded drug is protected by a patent to build the brand equity of the drug without direct competition of bioequivalent generics. Traditionally this brand equity is build among doctors using detailing, sampling, and journal advertising. The increase in direct to consumer advertising (DTCA) since 1997, when the regulations on DTCA have been loosened, has allowed firms to also actively build brand equity among patients. The resulting goodwill concerns differences in quality between the branded and generic drug and induces doctors to keep on prescribing branded drugs when generics are available (Caves, Whinston and Hurwitz 1991; Hurwitz and Caves 1988). These quality differences can arise by a higher quality control for branded manufacturers as generic manufacturers have fewer reputational assets to lose from lower quality control. Also quality perceptions of properties of branded drugs can be higher, such as formulation and stability. For example, branded drugs are perceived higher in effectiveness and lower in side effects, though the difference in quality perceptions has decreased over the last 40 years (Ganther and Kreling 2000; Hassali et al. 2009).

Hurwitz and Caves (1988) find that advertising before and after patent expiry preserves the branded drug’s market share, because it builds brand loyalty. Higher brand equity slows down the impact of generic entry (Kvesic 2008). However, while most branded drugs lose market share quickly after patent expiry, for some brands it pays off to keep marketing their brand, such as Intal and Coumadin (Parece, Tuttle and Hector 2004), especially when the technology is complicated and the brand’s sales are relatively low.

Rizzo (1999) finds that advertising decreases price sensitivity and thereby inhibits generic entry. Königbauer (2007) finds that over-investing in advertising before patent expiry has the potential to deter entry, but decreases social welfare. Scott Morton (2000) empirically investigates whether branded advertising creates a barrier to entry for generic drugs after patent expiration. She distinguishes between informative and persuasive advertising. The
latter merely persuades consumers of product differentiation between the brand and generic, while almost none exists, and may create a barrier to entry for generic firms. In contrast to earlier work investigating the relation between advertising and generic entry, she treats advertising as endogenous. She finds that when endogeneity is ignored, branded advertising deters entry. However, when correcting for endogeneity, advertising creates a barrier to entry by generic firms. This is in contradiction to the findings of earlier work.

Ellison and Ellison (2011) investigate strategic entry deterrence just before drugs lose patent protection. Using a sample of 63 drugs that lose their patent between 1986 and 1992, they find that investments to deter entry are nonmonotone in market size. For small markets, no investments are necessary to deter entry, while for large markets entry deterrence is impossible. Incumbents in medium-sized markets have lower advertising levels and are more likely to reduce their price and advertising near the patent expiry date.

In addition to patents, trademarks are available to protect the drug. They offer less intellectual property protection than patents, but may be renewed indefinitely. Trademarks can refer to the drug’s name, color, shape, etc. and signal quality and goodwill and reduce consumer search costs. The patent period gives firms time to develop trademarks in a monopoly market to retain the drug’s value even after patent expiry. For example, AstraZeneca successfully transferred the trademark of Prilosec (with the trademark: the purple pill) to its follow-up drug Nexium (the purple pill with racing stripes).

**Differentiation**

Firms can retain branded sales after generic entry by differentiating their drug from generics, which may justify their higher price. They can do that by providing more value of their drug than generics without extending the patent of the drug. They can introduce new flavors, new coatings, improved packaging, easy-to-swallow pills, or patches (Chandon 2004; Kvesic 2008). This can be supported by providing doctors with free samples, which are
typically not provided by generics. Another innovative approach is to offer other support services, such as a hotline for doctors. Branded manufacturers can also market the brand with a different message to patients or doctors, without actually changing the drug’s properties.

**Divestiture**

When a firm is not expecting a bright future for the drug after patent expiry, it can divest or milk the drug (Chandon 2004; Kvesic 2008). This is a viable alternative if a firm wants to free resources for other drugs in its portfolio. It involves cutting the drug’s marketing and R&D expenditures and selling or licensing the drug to another firm. The branded manufacturer may also increase the price targeting brand loyal customers and maximize short-term profits. Alternatively, a firm can milk the drug by focusing on segments where it has the biggest advantage over generics (e.g. hospitals, marketing-sensitive doctors).

**Branded generics**

The first generic obtaining US market approval through an ANDA obtains a 180-day exclusive marketing period for the drug. This temporary monopoly in the generics market allows the first generic to obtain large profits. However, during that period, branded manufacturers are allowed to introduce their own generics. The branded manufacturer needs no FDA approval to enter the market with a so-called branded generic – also referred to as authorized generic, pseudo-generic, or fighter brand. Large pharmaceutical firms often control subsidiaries that produce and market generics or they license the drug to a generic firm to compete against other generics (Chandon 2004; Kvesic 2008).

Branded generics are a regularly used strategy of pharmaceutical firms, especially outside the United States, to either deter generic entry or to capture a share of the generic profits (Berndt et al. 2007; Kamien and Zang 1999; Kong and Seldon 2004). Berndt et al. (2007) argue that there are two effects of branded generics on the price of generics. In the short run, competition increases in the generics market as branded generics are allowed to
enter during the 180-day exclusivity period for the first generic manufacturer. This results in a lower generic price during that period. In the long run, branded generics can deter entry, leading to higher long-run equilibrium prices for generics. In small markets, branded generics may even discourage generic manufacturers to submit an ANDA. Hollis (2003) finds for the generic market in Canada that branded generics have a substantial deterring effect on subsequent generic entries in medium-sized markets. Reiffen and Ward (2007) also find that branded generics deter entry in small and medium-sized markets. Depending on the market size they decrease the number of generic entrants by 1.7 to 2.4. They also find that branded generics increase equilibrium prices; on average, long-term generic prices increase by about 1% after the entry of a branded generic. This price increase leads to higher profits of the branded drug, up to 3.2%. Berndt et al. (2007) find that branded generics only lead to higher long-term prices when less than five generics enter the market, which is rarely the case in practice.

Kong and Seldon (2004) conclude in a theoretical study that introducing branded generics to deter entry is only in specific instances a profit-maximizing strategy. They suggest that firms should mainly introduce branded generics in large markets to capture part of the profits from the generics market.

Branded generics are often the first generic in the category and can benefit from a first-mover advantage. Grabowski and Vernon (1992) find that the first-moving generic has long-term advantages over followers. Reiffen and Ward (2007) report that the first generic entrant earns 19%-27% of total generic sales, while, on average, 14 generics enter.

**Switch to OTC**

The regulatory body sometimes allows drugs with a proven safety under self-medication circumstances to be available over the counter. Similar to prescription drugs, in the United States, the FDA regulates the approval and marketing claims for OTC drugs and
they require an approved label with drug facts for patient education. There are two different forms of OTC products: (i) those that may only be dispensed after a pharmacy employee has assessed the needs of the patients and has given some patient education, (ii) those that are just like any other consumer product and are freely available in store. In case the OTC drug has a new indication, dosage, or form, it is eligible for three years of market exclusivity.

OTC products make up 28% of unit prescriptions in the United States, comparable to other countries (Danzon and Furukawa 2008). The advantage of OTC drugs is that they can have high sales for a prolonged period of time. For example, Listerine is available for over 100 years and still successful. The number of prescription drugs approved for OTC usage has risen since the nineties (Ling, Berndt and Kyle 2002). Older classes of H$_2$-antagonists (e.g. Tagamet, Zantac) and antacids are well-known examples of prescription drugs that are converted to OTC. In Europe, switching a prescription drug to OTC can be a good strategy as then it can then be advertised to consumers (Kvesic 2008). However, also in the United States where DTCA is allowed for prescription drugs, OTC products are heavily advertised.

An OTC drug has the potential to expand the market for its molecule. In addition, it has two opposing effects on the manufacturer. It can cannibalize sales of the branded drug, but the firm can also benefit from spillover effects between the prescription and OTC drug. Often, the cannibalization is limited to a certain extent as OTC drugs are mainly available in lower dosages, while higher dosages are still prescription only. Spillover effects between the OTC and prescription drug are also likely, as OTC drug can benefit from the brand equity of the prescription drug and the firm can benefit from spillover effects in promotion.

Berndt, Kyle and Ling (2003) explore the effects of making prescription drugs available over the counter for four drugs in the H$_2$-antagonist category. They focus on the impact of OTC switches on the sales of the branded prescription drug and the joint sales of the OTC drug and the branded prescription drug. They find that the amount of
cannibalization and the spillover effect between the OTC and the prescription drug varies across brands, depending on whether generic alternatives are available for that drug.

Ling, Berndt and Kyle (2002) find spillover effects of marketing prescription drugs on OTC drug sales, but not vice versa. These spillover effects are found for detailing and not for DTCA. They also find an order-of-entry effect for OTC drugs. Later entrants in the OTC market compensate for this by spending a higher percentage of their sales on marketing.

**Summary of marketing strategies**

Marketing strategies to fend off generic entry are relatively easy to implement and mainly have a short-term impact. Pricing and promotion can decrease the extent of generic entry in a limited way. Price decreases to deter entry are infrequent in practice and promotion has been found to deter entry in medium-sized markets. After patent expiry, firms often maintain or increase the branded drug’s price and focus on the price-insensitive customers to retain a profitable market share. Research to date on pricing and promotion mainly describes the rationale behind branded price changes around patent expiry. Future research is warranted on the optimal pricing and promotion of a branded drug around patent expiry, balancing both its competitive effects on generic and branded competitors and its effect on entry deterrence. Empirical studies on the profitability of these strategies are also welcome. Future research can also focus on the impact of trademarks before patent expiry on the post-patent success of a branded drug and how this influences its pricing and promotion strategy.

Research into differentiation strategies and divesting the drug is limited to case evidence. Future research can focus on the impact of various differentiation strategies on sales for the branded product. It is also valuable to investigate theoretically and empirically the optimal pricing and promotion path to divest a drug. This is especially relevant when a firm has multiple related products that may cannibalize each other.
The introduction of branded generics has two potential effects on the market. First, they can deter entry, but its effect on long-term prices is limited and works mainly in small to medium-sized markets. Second, a branded generic can provide the branded manufacturer with a profitable share of the generics market. The latter applies mainly to large markets with many generic entrants. Further research is necessary on branded generics’ influence on the branded drug and on how to price and market both. Furthermore, it is valuable to investigate whether preannouncements of branded generics is an effective entry deterrence mechanism.

Switching a prescription drug to OTC status is a viable alternative for some drugs. The challenge for empirical analysis on the impact of such a switch is that different datasets need to be combined, prescription drug sales and OTC sales, which are collected by different data providers (Berndt, Kyle and Ling 2003). This is an important reason for the lack of research in this area and interesting questions remain to be answered to assess the impact of switching a drug to OTC status. For example, how to price the OTC drug compared to the branded drug and compared to possible generic alternatives. What is the optimal moment to switch to OTC? How does brand equity transfer from the prescription drug to the OTC drug? Should the OTC brand name be related to the prescription drug?

**Research and Development Strategies**

R&D strategies build on an existing drug in the market. Development strategies mainly build on reputational assets, as they are extensions of an existing drug. They make use of a patent extension or extended market exclusivity of several years. They improve on convenience for the patient, increase drug effectiveness, reduce side effects, or are approved for new indications. Research-oriented strategies build more on the knowledge assets of a firm, require extensive research, and new drugs resulting from this strategy often qualify for a new patent on the molecule.
Ganuza, Llobet and Domínguez (2009) show that pharmaceutical firms target their R&D on small innovations, such as product-line extensions. This is driven by the low sensitivity of demand. Indeed, a large part of newly approved drugs are line extensions.

**New indications**

As existing drugs have known pharmacokinetic profiles and side effects, new indications for them are relatively cheap to develop. The process of finding new uses for the drug outside current indications is sometimes referred to as drug repositioning and requires additional clinical testing (Ashburn and Thor 2004). The new indications have the advantage of starting with a Phase II trial which saves almost 40% of the costs of clinical testing (Chong and Sullivan 2007). New indications enlarge the market potential of a drug and can extend the market exclusivity period up to three years through an sNDA (Bhat 2005; Dubey and Dubey 2009; Kvesic 2008). It is a widely used strategy and 84% of the top 50 drugs in 2004 has obtained additional indications after approval (Sandner and Ziegelbauer 2008).

One specific way for firms to extend the market exclusivity period of a drug by six months is to investigate, before patent expiry, the effectiveness of the drug in children. This pediatric exclusivity is independent of the success of the study and must be requested by the FDA (see for the guidance document: FDA 1999). Upon request, this is a standard move for successful drugs. Firms can increase the chances of receiving such a request by proposing pediatric studies to the FDA. For example, sildenafil (Viagra) was initially developed for angina, but in 1998 approved for erectile dysfunction, and in 2003 for pulmonary arterial hypertension under the brand name Revatio. In addition, the manufacturer tested the drug on a rare lung disorder for children to receive an additional six months of pediatric exclusivity.

Huskamp et al. (2008) find that promotional expenditures of drugs in the selective serotonin reuptake inhibitor (SSRI) category increased after approval for a new indication. Depending on the new indication, firms increased either detailing or DTCA expenditures.
New indications are usually marketed under the same brand name and hence the brand equity of the drug can be leveraged to the new indication. If the new indication is very different from current indications, firms can opt to market it under a new brand name (e.g. Viagra and Revatio, both sildenafil; Zyban and Wellbutrin, both bupropion; Proscar and Propecia, both finasteride; Prozac and Sarafem, both fluoxetine). Drugs with multiple indications have an increased chance of competing in different markets and to a different set of competitors. Firms should then carefully consider the pricing of the drug in order to be competitive in the various markets.

Reformulations

Reformulations of a drug use the same active ingredient as the original drug, but the formulation is changed to improve compliance, side effects or efficacy. This strategy can involve new forms or dosages and requires new clinical tests. Reformulations have a shorter approval path than NMEs (Fleming and Ma 2002) and upon approval receive at least three additional years of market exclusivity through a sNDA (Bhat 2005). Reformulations often involve technical challenges, which sometimes can be patented, making it harder for generic firms to copy or design around.

Time-release versions of a drug are a popular reformulation and make up 8% of unit sales of prescription drugs in the United States (Danzon and Furukawa 2008)\(^7\). They ensure a slow and controlled release of the drug in the body and provide the advantage of fewer dosages per day (compared to instant-release formulations) and fewer side effects. Other emerging technologies are site-specific drug delivery, depot formulation, and inhalation drug delivery (Dubey and Dubey 2009).

60% of newly approved drugs are reformulations (Dubey and Dubey 2009; Huskamp et al. 2008; Sandner and Ziegelbauer 2008). The cost of introducing a reformulation is

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\(^7\) Time-release technology is also referred to as sustained release (SR), sustained-action (SA), extended release (ER, XR or XL), controlled-release (CR), modified-release (MR), or continuous-release (CR).
estimated to be $10-$50 million (Bhat 2005). The reformulation typically builds on the brand name of the original drug (e.g. Effexor XR is a reformulation of Effexor). When the reformulation is approved, only the reformulation receives the additional market exclusivity. Hence it is important for firms to differentiate their reformulation from the original drug and switch patients to the reformulation in order to benefit from the additional market exclusivity. Huskamp et al. (2008) find that promotional expenditures for the original brand decrease substantially when a reformulation is introduced.

**Combination drugs**

Combination drugs are an increasingly popular lifecycle extension strategy (e.g. Advair, Caduet, Vytorin), with worldwide sales in 2009 of over $30 billion. Combination drugs are two or more active ingredients that are physically or chemically combined to produce a single pill, inhaler, injection, or patch (Herrick and Million 2007). In some circumstances, firms are allowed to co-package drugs (Evans and Salinger 2007); however, this is more common for OTC drugs. Combination drugs are often based on two or more ingredients already on the market and qualify for a new patent. It is required for approval that the combination drugs provides an improved treatment for at least some type of patient, compared to the single components. The approval process of a combination drug depends on the experience with the single components. If the single components are already approved, drug agencies move more swiftly. For example, the FDA may allow the combination drug to start testing in phase three.

While empirical research on the sales success of combination drugs is lacking, they can be considered as a form of product bundling (Stremersch and Tellis 2002). Bundling can be done to leverage market power from one to another market, but also to provide a quality signal, which lowers the informational costs for customers.
Next-Generation drugs

An alternative way to use R&D to build on an existing drug is to develop next-generation drugs. Their development builds on the mode of action and pharmacology of the first generation product and needs to demonstrate significantly improved properties. It changes the underlying chemical structure of the active ingredient and requires a NDA.

Research on the success and marketing of next-generation drugs is lacking and evidence on their effectiveness to extend the product lifecycle of a drug is limited to case studies (e.g. Conley, Wolcott and Wong 2006). However, in press these strategies are widely debated. On the one hand, the next-generation drug can build on the brand equity of the previous generation drug, while on the other hand it may need to differentiate itself enough to induce customers to switch. Two well-known examples are Nexium and Clarinex. Claritin is the first generation product and a metabolized version of the drug was approved to the market as an NME (Fleming and Ma 2002). The next-generation drug was named Clarinex, clearly positioning it as the ‘next Claritin’. Nexium is a successful single-isomer version of first generation drug Prilosec; however, it was positioned as a new drug. The link between the two drugs was made through the trademark ‘the purple pill’ and Nexium was strongly differentiated from Prilosec in the marketing communications.

Summary of R&D strategies

New indications and drug reformulations are frequently used lifecycle extension strategies. New indications require no change to the existing product and usually keep the same brand name. One challenge for new indications is that the set of competitors for a product may change to which a firm should adapt. In case the new indication is very different from existing indications, a firm may consider marketing it under a new brand name. Reformulations build on an existing drug and brand name. They are line extensions and firms typically shift their promotional expenditures from the original drug to the reformulation.
While widely used in practice, research into the success of new indications and reformulations is limited and worthwhile for future research. The optimal timing of the introduction of a reformulation and new indication is also a very important open question, especially in relation to the patent expiry date of the original drug.

The research strategies that require a longer-term investment, such as combination drugs and next-generation drugs, have almost not been researched in the academic literature. While a substantial literature exists on how to develop this kind of drugs, I have identified no study that evaluates the impact of the pricing and promotion of these drugs on market success. While the number combination drugs is relatively large (over 100 in the last decade), the number of next-generation drugs is more difficult to identify and classify. Both provide interesting marketing problems as they are strongly related to the components of the combination drug or the previous-generation drug, which are already on the market. The challenge for research is to identify how firms should price and promote such a portfolio of interrelated drugs, taking into account spillover effects and cannibalization. Another major challenge is how to position a next-generation drug compared to the original drug. Some have chosen to explicitly position the next-generation drug as a new product (e.g. Nexium), while others have positioned it more as a reformulation (e.g. Clarinex, Glucovance).

**Legal Strategies**

A drug consists of its main active ingredient and excipients to make the active ingredient work, delay its absorption in the body, and create the taste of the oral drug. Both the active ingredient and the excipients can be patented and firms use these to protect their intellectual property. The United States Patent and Trademark Office (USPTO) grants three types of patents: (i) utility patents to protect new processes, machines, articles and compositions of matter, (ii) plant patent to protect new asexually reproduced plants, (iii)
design patents to protect novel ornamental designs of manufactured articles. New drugs usually receive utility patents. The active ingredients of drugs are patented long before market approval, typically when phase two testing starts. This involves the composition of matter and protects the constituent elements of a drug and their specified chemical formulas. However, other patents are used as well to protect the branded drug, such as the different formulations used in treatment (chemical variants), methods of manufacture, methods of administration, and specific indications of use. However, often generic firms can ‘design around’ such patents. Infringements on the composition of the matter claim (or chemical claim) are easier to detect than on the other type of patents.

**Patenting strategies**

Firms can extend the lifecycle substantially by having a good patenting strategy (see Burdon and Sloper 2003 for various examples). In 2005, firms had an average of ten patents on a drug, compared to an average of two patents in 1995 (Frank 2007b). As a result the length of the nominal patent period for branded drugs has increased (Hemphill and Sampat 2011). At the same time, Hemphill and Sampat (2011) find that the fraction of drugs receiving patent challenges has increased; they are challenged sooner, and drugs with higher sales are challenged more often. Bruce (2003) provides various patent cases for pharmaceuticals. Patents also deter entry as the costs to invent around, license, or challenge the patent can be large (e.g. in the software industry, Cockburn and MacGarvie 2011).

**Generic settlements**

Manufacturers can settle with a generic manufacturer that challenges the patent on the branded drug, to drop the patent challenge or delay generic entry (Bulow 2004). These settlements involve a payment of the branded manufacturer to the potential generic entrant. These are also referred to as sweetheart deals and can be very profitable. It works especially for the first generic manufacturer that has a 180-day exclusive marketing period. There is a
clear incentive for branded manufacturers to pay the generic manufacturer to delay entry, due to the higher margins for the branded drug. These settlements are highly disputed by the antitrust authorities (e.g. FTC) and society, but are not immediately forbidden by law. Several cases have been in court, with mixed outcomes (Forden 2011; Frank 2007b).

Summary of legal strategies

The biggest part of the profits from pharmaceutical drugs is earned during the period in which the drug is protected by patents. Hence, firms can extend the patent on a drug or delay generic market entry to obtain extra profits. There are two main ways of delaying generic entry (see Shuchman (2006) for a case discussion of these strategies for Plavix). Over the last 15 years, firms have adopted a strategy of multiple patents to protect a branded drug, increasing the market exclusivity period of the drug, and firms are involved in settlements with generic manufacturers to postpone their market entry. Research comparing the return on these legal strategies to other lifecycle extension strategies would help firms to make tradeoffs on which strategy to prioritize.

Conclusion and Suggestion for Future Research

Lifecycle extension strategies in the pharmaceutical industry are becoming a popular way for pharmaceutical firms to make profits. While lifecycle extension strategies have existed for some time, the rising costs of developing a new drug and the increasing impact of generics, has lead firms to increasingly focus on lifecycle extensions. The academic literature reviewed in this chapter has focused mainly on the determinants and consequences of generic entry. Strategies to extend the drug’s lifecycle have received less attention. Further research in these areas is warranted to increase our understanding of how various strategies work, which strategies are successful, and why they are successful. Future research can utilize the
enormous amounts of data available on drugs. The FDA Orange book contains detailed information for each branded and generic drug, including the approval and expiry date for every patent, the manufacturer, the form of the drug, line extensions, and combination drugs. The FDA website contains information on extra indications and label changes for every drug. Organizations such as the Tufts Center for the Study of Drug Development and the Kaiser Family Foundation have extensive data available on, respectively, approved drugs in the United States and Europe, and health outcomes. Data providers like IMS Health, Kantar Media, and Wolters Kluwer have detailed information on sales, price, and marketing expenditures. While detailed information on sales and marketing is often limitedly available, publicly available data at a more aggregate level is provided by, for example, IMS Health and www.drugs.com.

Marketing strategies to extend the lifecycle of drugs nearing patent expiry can benefit from the extensive literature on marketing strategies in other industries. Insights on optimal pricing, promotion, and divestiture paths can be derived using theoretical models and dynamic empirical models. However, a large cross-sectional research on various moderators of pricing and promotion strategies around patent expiry is necessary. Such study should explore how the success of these marketing strategies depends on the competitive landscape, trademarks of the branded drug, brand loyalty, chronic or acute disease, insurance type of patients, etc. Branded generics are a longer-term strategy which has already received some attention in the literature, but a large-scale empirical study that measures its impact in practice is valuable. Switching a prescription drug to become available over the counter requires the combination of different data sources and is a topic with ample opportunities for future research.

For the R&D strategies, many open areas for future research exist. In addition to extra research on the what-question – what strategy should a firm use and what is the impact of
such a strategy – the when-question is very important. When should a firm implement the reformulation or combination drug to maximize the return on investment? Is it optimal to make a combination drug available when the single components are still under patent, or should a firm launch it near the patent expiration date of a single component? Research on the market impact of reformulations, combination drugs, and next-generation product is lacking in general. They are all a form of line extensions and questions on brand name, spillover effects in marketing, and cannibalization are important for future research to address.

Legal lifecycle extension strategies are also widely used by pharmaceutical firms. Marketing research can benefit from an improved understanding and clear outlining of how the regulations on patent extensions and market exclusivity impact firms decisions.

The discussion on pharmaceutical lifecycle extension strategies in this chapter has focused on nonbiologic drugs. These differ substantially from biologics due to their complexity, which makes biologics more expensive and it is harder to produce therapeutically equivalent generic versions of them. However, the number of approved biologics is rising substantially and their share of pharmaceutical sales is increasing (Munos 2009). Regulations on the approval of biologics that are biosimilar to drugs already on the market, is not well established yet and little research exists on their impact. In 2005, the EMA has published guidelines for biosimilars that give product-specific guidelines for their approval. In 2009, US congress has passed the Biologics Price Competition and Innovation (BPCI) Act, allowing the FDA to approve biosimilars. The FDA is currently working on guidelines for an approval path for biosimilars (Kozlowski et al. 2011). The guidelines will be stricter than the approval of generic nonbiologics. However, when the patent on a biologic expires, biosimilars will enter if the market is attractive enough. Compared to nonbiologics, production and entry costs of biosimilars are higher, limiting the number of generic entrants.
Hence, in the future biologics are still likely to face less competition after patent expiry, making them an attractive alternative to nonbiologics and a very important topic for research.

Most strategies to extend the lifecycle involve interdisciplinary knowledge on marketing, R&D and regulations. This makes it challenging to investigate various lifecycle extension strategies in-depth. The marketing and economics literature have largely overlooked the impact of R&D and legal strategies. Plenty of research exists on the technical issues around R&D strategies and the legal issues surrounding the regulations and law on drugs, but is not discussed in detail here. Research on pharmaceutical lifecycle extension strategies would benefit from researchers or interdisciplinary research teams that are able to jointly assess the impact of marketing, R&D, and legal strategies. Finally, research on pharmaceutical lifecycle extensions would benefit tremendously from a study comparing the impact of the various strategies. One way to do that is to collect information on the various strategies and some moderators and relate those to the stock returns of pharmaceutical firms.
References


### Table 1: Overview of Pharmaceutical Terminology and Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Explanation</th>
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<tr>
<td>ANDA</td>
<td>Abbreviated new drug application: contains data that provides for the review and ultimate approval of a generic drug product. These are not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent.</td>
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<tr>
<td>Bioequivalence</td>
<td>The absence of a significant difference in the rate and extent to which the active ingredient/moiety in pharmaceutical equivalents (i.e. same active ingredient, dosage form, route of administration and strength) becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.</td>
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<tr>
<td>NDA</td>
<td>New drug application: an application for a new drug approval containing data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, the product may be marketed.</td>
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<tr>
<td>NME</td>
<td>New molecular entity: an active ingredient that has never before been marketed in any form.</td>
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<td>OTC</td>
<td>Over-the-counter: drugs classified as safe and effective for use by the general public and which can be obtained without a doctor's prescription.</td>
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<td>sNDA</td>
<td>Supplemental new drug application: an application to allow a firm to make changes in a product that already has an approved new drug application (NDA).</td>
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<td>SPC</td>
<td>Supplementary patent certificate: extension of a patent used by the European Union.</td>
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<td>Article</td>
<td>Goal</td>
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<tr>
<td>Hurwitz and Caves 1988</td>
<td>Investigate the impact of goodwill on branded drug share and the impact of the generic price and promotion on the branded drug’s share.</td>
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<tr>
<td>Caves, Whinston and Hurwitz 1991</td>
<td>Identify the patterns displayed by branded and generic drugs' prices, market shares, and quantities sold, as well as branded drugs' advertising.</td>
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<tr>
<td>Grabowski and Vernon 1992</td>
<td>Investigate the impact of generic entry on generic and branded drug prices, as well as the determinants of generic entry.</td>
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<tr>
<td>Frank and Salkever 1997</td>
<td>Price response of generic and branded drugs to generic entry.</td>
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<td>Article</td>
<td>Goal</td>
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<tr>
<td>Bae 1997</td>
<td>Determine factors that influence the speed and likelihood of generic drug entries.</td>
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<tr>
<td>Ellison et al. 1997</td>
<td>Compute own and cross-price elasticity between branded and generic drugs.</td>
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<tr>
<td>Scott Morton 2000</td>
<td>Entry decisions of generic firms into markets opened up by patent expiration.</td>
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<tr>
<td>Berndt, Kyle and Ling 2003</td>
<td>Pricing and marketing for branded drugs around patent expiration.</td>
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<td>Article</td>
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<tr>
<td>Wiggins and Maness 2004</td>
<td>Determine the relationship between price and the number of generic sellers.</td>
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<tr>
<td>Hong et al. 2005</td>
<td>Test whether market entries of new extensions are associated with market success of original branded drugs and whether branded drugs exhibit price rigidity to generic entry only when they are extended.</td>
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<tr>
<td>Reiffen and Ward 2005</td>
<td>Understand how competition evolves in the generic drug industry.</td>
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<tr>
<td>Saha et al. 2006</td>
<td>Understand the interactions between generic entry, prices, and market shares.</td>
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<tr>
<td>Article</td>
<td>Goal</td>
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<tr>
<td>Gonzalez et</td>
<td>Study how doctors and doctor characteristics impact competition among</td>
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<td>al. 2008</td>
<td>molecules in a therapeutic class, when one of the drugs loses its</td>
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<td></td>
<td>patent and generics enter.</td>
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<td>Regan 2008</td>
<td>Study the effect of generic entry on post-patent price competition.</td>
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<tr>
<td>Ching 2010</td>
<td>Investigate the dynamics of demand for prescription drugs after</td>
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<td>patent expiration.</td>
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Notes: Two important regulatory changes may have substantial impact on the results in different time periods: 1) the Hatch-Waxman Act in 1984, 2) the change in the regulations on DTCA in 1997.
Figures

Figure 1: The Number of New Drug Approvals between 1950 and 2010 is Relatively Stable.
Figure 2: Pharmaceutical Lifecycle Extension Strategies Classified According to Their Impact.

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<th>Short-Term Impact</th>
<th>Medium-Term Impact</th>
<th>Long-Term Impact</th>
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<tr>
<td><strong>Marketing</strong></td>
<td>Pricing</td>
<td>Differentiation</td>
<td>Switch to OTC</td>
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<td></td>
<td>Promotion</td>
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<td>New indications</td>
<td>Combination drugs</td>
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<td>Reformulations</td>
<td>Next-generation</td>
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<td>Generic settlements</td>
<td>Patenting strategy</td>
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Source: adapted from Sandner and Ziegelbauer (2008).