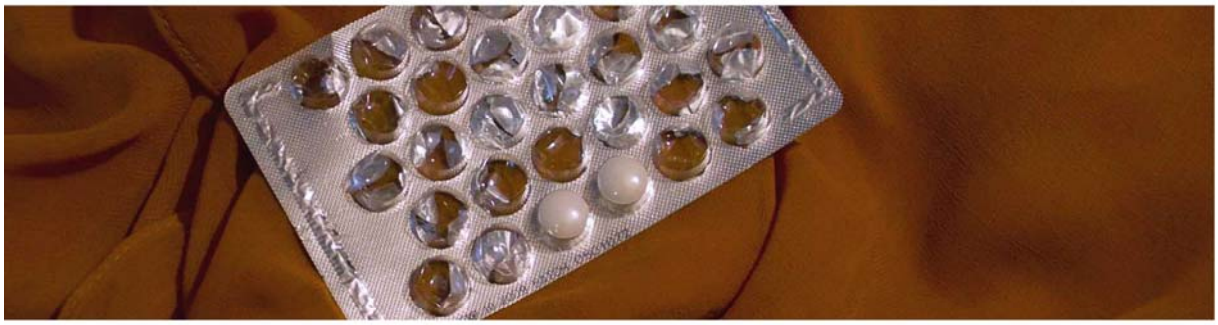
Bachelor Thesis

Generics:
A Threat to Innovation in the US Pharmaceutical Industry?



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Summary

The pharmaceutical industry is one the most profitable industries, but innovative companies are in a period where innovation seems to stagnate. The road to new drug development has become increasingly more complex due to regulations and rising costs. Estimates for the cost of one new FDA approved drug have risen from US$ 802 million in 2003 to US$ 1,318 billion in 2007.

Not only drug development costs have increased, but also healthcare expenditure. If health expenditures continue to rise and no appropriate action is taken, governments might not be able to fund the healthcare needs of every individual.

A possible action is the use of generics, therapeutically equivalent to branded drugs, but at a fraction of the costs. This helps the governments to contain healthcare costs. However generic firms, typically, do not aid to the development of new therapies and drug development of conditions to which there is no treatment available. Too abundant use of generics reduces the motivation for branded firms to innovate, as it would be harder to recoup investments. It might be that generics seize a share large enough to threaten innovation in the US pharmaceutical industry.

Drug development cost has increased over the years, while the patent protection system -on which the pharmaceutical industry heavily relies- seems not keep up with current developments. As Governmental regulation continues to strongly promote usage of generics, pharmaceutical companies can combat generics through various marketing strategies and interfirm agreements, however this may not be enough to improve R&D productivity.

Introduction

Ask a number of people in the street to name three medicines, this wouldn't be too difficult to answer. Then ask to name three companies who produce medicines, now this would be a real challenge.
The pharmaceutical companies are often overlooked and almost taken for granted by consumers, but nonetheless are of great importance in the healthcare system chain for every country in the world. They are the suppliers of drugs, they research, develop and if successful put it on the market.
The pharmaceutical industry is a multi billion dollar business, which could be quite tempting to enter. More competition should mean lower prices, translating into lower healthcare costs.
The global population grows and ages, and older people consume more healthcare. Governments will have to devote an increasingly larger proportion of their budget to healthcare expenditure. Health expenditure in the US was approximately 16% of GDP in 2006 and is expected to rise to 20% (see figure 1). If healthcare costs keep increasing, without efforts to contain healthcare expenditure, governments would not be able to fund the healthcare needs in the future[26)].

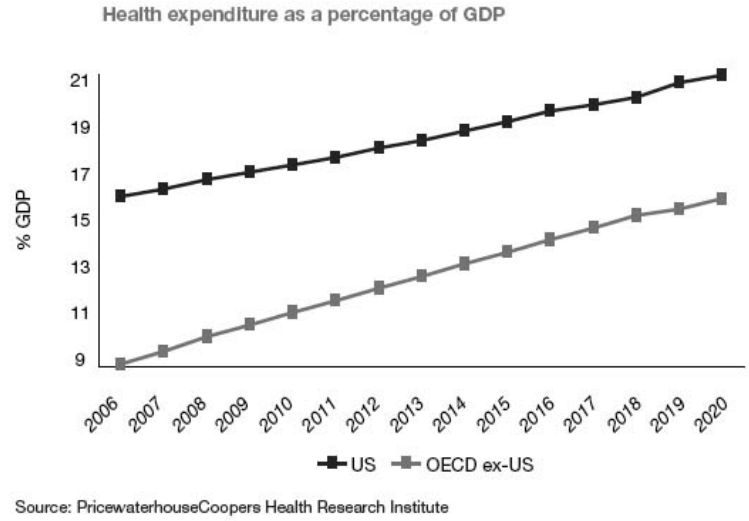

Figure 1

A method to lower healthcare costs might be the use of generic drugs. Generic drugs are therapeutically equivalent to brand-name (the company who initially put it on the market) drugs, but may differ in the non-medical ingredients of the drug[5)].

Paxil for example is an antidepressant, the active ingredient is paroxetine. The price of Paxil on drugspark.com for 40mg-90Tabs is $395. The generic equivalent which also contains paroxetine costs $190 (40mg-90Tabs). The generic is therapeutically the same as the brand-name drug (Paxil), but 52% cheaper!

In a study by Saha et al. (2006) of 40 oral prescription drugs where the first generic entered, it is shown that after a period of 12 months prices dropped approximately 50% of the brand name drug. So why even bother buying the brand name drug when both are available?

Society desires more diseases to be cured and better medicines with fewer side effects.

This calls for innovation, but innovation is typically done by the companies who produce brand-name drugs. Innovation involves a lot of research and that can only be done if there are enough revenues made to recoup investments made for developing a drug. The research costs to make one drug will typically run in millions of dollars and the return on the investment can only be assured if there is a well working patent system available.

1. The Pharmaceutical Industry and Innovation

According to Fortune magazine[1)] the pharmaceutical industry belongs to the second most profitable industry in 2008 (profits as return of revenues), taking 17.7% of all profits made by the listed industries.

The IMS reported a global pharmaceutical sale of $773 billion in 2008 [2)] almost double figures compared to 2001 as shown in table 1. However growth has been declining, this issue is addressed in the chapter *Current Sitiation of The Pharmaceutical Industry*.

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Global Pharmaceutical Sales, 2001 – 2008

	2001	2002	2003	2004	2005	2006	2007	2008
Total World market (current US$ in billions)	393	429	499	560	605	648	715	773
Growth Over Previous year ($Constant US$ Growth)	11.8%	9.2%	10.2%	7.9%	7.2%	6.8%	6.6%	4.8%

Source: IMS Health Market Prognosis (includes IMS Audited and Unaudited markets)
All information current as of March, 2009

Table 1.

Under regulations of the US and other nations, there is a distinction between prescription (also known as ethical) drugs and 'over the counter drugs' (OTC) [9)]. Ethical drugs are only available with a prescription from a physician to a pharmacist. OTC drugs can also be obtained without a prescription from retailers.

As most innovation is done by the ethical pharmaceutical industry, this thesis will concentrate more towards this sector. Expenditures on ethical drugs are rising and were US$227.5 bn[2)] in 2008 in the United States. Although ethical drugs spending has been a relatively small proportion of national health care spending (10% in 2006, compared to 31% for hospitals and 21% for physician services), it has been one of the fastest growing components[8)].

The ethical pharmaceutical industry is important, not only for its economic size, but also for the benefit it delivers to users. The industry has been transformed structurally since the 1940s

from a producer of selected chemicals to a research-orientated sector that makes a major contribution to the technology of health care[7)].

Two important preconditions for innovation in this industry are market-based pricing and intellectual property protection[4)]. France is a good example why (as far allowed by governmental regulations) market-based pricing is important and how too strict price regulations can work against innovation. In the second half of the 1960s, French pharmaceutical companies matched U.S. firms in producing new drug substances – 92 for France, 93 for the United States[4)]. This was double the innovation output for German firms in the same period, which in turn was double the output of the United Kingdom[4)]. Over the next three decades, U.S. innovation continued to outpace all others[4)]. Production of new drugs held steady in the United Kingdom, declined sharply in Germany, and all collapsed in France[4)]. In the five-year period from 1990 through 1994, US firms produced 85 new drugs[4)]. French firms produced 14[4)]. How come French innovation collapsed?

A great part of the answer has to be the impact of price controls[4)]. The French system aims to force the lowest possible unit price for pharmaceuticals, and in pursuit of this, it takes a very deliberate aim at innovation, by forcing price restrictions so harsh French pharmaceutical firms had almost no incentives to innovate anymore[4)]. When a first mover product was approved, its price was set based, in part on its expected sales volume[4)]. If sales exceeded expectations, the maker was required to cut the price to compensate the costs for the government to reimburse[4),] In other words, French firms were punished if innovation was successful.

The drug that the innovating company (first mover) brings to the market can be classified as a brand-name drug, these are protected by intellectual property rights on the active ingredient (or chemical entity). The generic drug does not hold a patent on the active ingredient, however it can hold one on the formulation.

Before a new chemical entity (NCE) can be approved, the manufacturer has to comply with certain policies and procedures. The drug maker first has to file an application for Investigation of New Drug (IND) for the NCE, which has to pass through three different phases, each costing millions for the investing company. This count for each NCE even if it is not sure that the NCE will result in a FDA approved drug for the investing company.

In the end only a few will be produced as a drug and make it to the market. It is expected that this drug will earn back its research costs, the costs of all the failed NCE's and will make a profit for the innovator's risky investment. Because of its importance towards innovation, this

thesis will be more elaborate on how a drug is introduced to the market the chapter of *Regulation and New Drug Development*.
Without an intellectual property protection system, another company could compete the day the drug is taken to market at a fraction of the price the innovator would ask. This would result into huge losses to the innovating investor, who accounted for all the research investments in a drug that would probably be never profitable.
Because the patent system has an important effect on innovation, creating a legal monopoly of an innovative product[7)], which in most industries would not be desirable, this thesis will also be more explanatory on this system in the chapters *Generic Entry* and *Paragraph IV filing*.

2. Drug Development

2.1. Regulation and New Drug Development

Most nations have created their own institutions to make sure that new drugs put on the market are safe and efficacious. In the European Union for example evaluation and authorisation of medicinal products are done by the EMEA (European Medicines Agency). Regulatory control varies among nations, this thesis will focus on the United States.
In 1906 president Roosevelt signed the Food and Drug Act, also known as the Wiley Act. This act imposed regulations on product labelling and required the standards set by the US Pharmacopeia were met.
The basis of this Act was not pre-market approval and had major shortcomings. An eyelash that blinded numerous women and other products that were hazardous to health were still legal under this law. After a drug maker put a highly toxic solvent in their (untested) product and over hundred deaths occurred resulting of that drug, the 1938 Food, Drug, and Cosmetic Act was passed. Manufacturers now had to prove to the Food and Drug Administration (established in 1930) their drug was safe before it could be sold onto the market.
In Europe a new tranquilizer, thalidomide was approved and used to combat morning sickness. Unfortunately not tested thorough enough, resulted to the birth of thousands deformed babies[9)]. This event had the U.S congress look more closely to the flaws of the law and led to the Kefauver-Harris Act. The new law commanded new drugs must not only be safe, but also

efficacious before put onto the market, giving the FDA more power and control over drug testing and marketing. During pre-clinical development a manufacturer now had to prove the drug was relatively safe to use on humans and decide whether the compound would be feasible for further commercial development. When the drug maker (or its sponsors) identifies the compound as feasible, they can focus on data collection and make sure that humans are not exposed to unreasonable risks in early clinical trials. If the manufacturer can submit evidence of toxicity levels in dosage of the anticipated level of usage, which will show it is reasonably safe for humans, they can file an application for Investigation of New Drug (IND) to the FDA to test the new chemical entity (NCE) in human beings. The IND application must cover three important issues:

• Animal pharmacology and toxicology studies, that consists preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans[11)].

• Manufacturing information, which gives information about the composition, stability and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug[11)].

• Clinical protocols and investigator information in which detailed protocols are proposed for clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks and information about the qualifications of clinical investigators (generally physicians), to assess whether they are qualified to fulfill their clinical trial duties[11)].

The FDA has 30 days to judge the IND, in this period the applicant cannot begin clinical trials yet. If the manufacturer obtains approval from the FDA, they may undertake clinical trials and three phases are set into motion.

The first phase trials consist of studies to determine the metabolism and pharmacologic actions of drugs in humans, the side effects associated with increasing doses, and to gain early evidence of effectiveness[12)]. This will include a small number of usually healthy people, ranging from 20 to 100 subjects[27)].

The next phase will conduct tests on patients who suffer the targeted disease. These tests are designed to determine the short-term side effects and risk. Numbers in Phase II testing are ranging from 100 to 500 patients[27)].

The final pre-approval phase, phase III, are designed to establish the efficacy, side effects that infrequently occur, evaluation of benefit-risk relationship and provide a basis for physician labeling[12]. These are large scale test and patients number in thousands[27].

When the manufacturer beliefs the drug is safe and efficacious, it can compile the results in an application for a new drug approval (NDA). This will be reviewed and assessed by the FDA before the drug can be marketed. After approval, FDA may require specific phase IV studies to obtain more information about the medicine [27]. The manufacturer may research additional indications and the manufacturer must always monitor and report adverse events to the FDA. In 2007 US Congress gave the FDA more resources and authority to enhance drug safety[27]. This includes new authorities and funds to require companies to conduct post-market studies and clinical trials, make safety labeling changes and develop and implement 'Risk Evaluation and Mitigation Strategies' [27]. Congress also gave the FDA new resources and authorities to improve post-market risk identification and analyses[27]. Figure 2 shows the development process and how risky the drug development progress is. Out of 5000 to 10,000 compounds only one is approved. In a study by Dimasi et al.(2003) it is showed that the average length from clinical testing to marketing approval is 90.3 months.

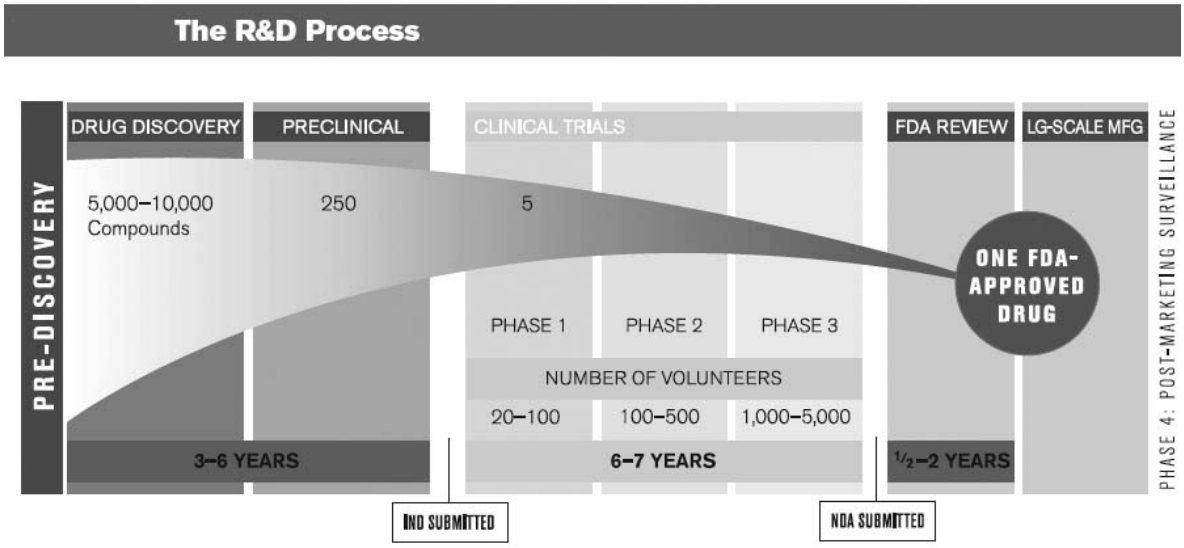


Figure 2, Source; PhRMA Industry Profile 2009

2.2. Drug Development costs and Life Cycle

The process of drug development is a very lengthy and risky process and requires capital from the drug maker or its sponsor. Table 2 provides an insight of the expenses and probabilities to cover and pass each phase.

Average out-of-pocket clinical period costs for investigational compounds (in millions of 2000 dollars)[a]

Testing phase	Mean cost	Median cost	Standard deviation	N[b]	Probability of entering phase (%)	Expected cost
Phase I	15.2	13.9	12.8	66	100.0	15.2
Phase II	23.5	17.0	22.1	53	71.0	16.7
Phase III	86.3	62.0	60.6	33	31.4	27.1
Long-term animal	5.2	3.1	4.8	20	31.4	1.6
Total						60.6

[a] All costs were deflated using the GDP Implicit Price Deflator. Weighted values were used in calculating means, medians, and standard deviations.

[b] *N*: number of compounds with full cost data for the phase.

Table 2, Source; J.A. DiMasi et al./ Journal of Health Economics 22 (2003) 151-185

Each consecutive phase is characterized by increasing costs. This can be explained by the scale of testing.

Phase III involves large scale testing including thousands of patients, while phase I and II compounded are usually composed of a few hundred subjects. Probability of making it into the third phase is only 31.4%, which means that 68.6% of the IND applicants fail.

Note that these compounds were already approved for IND, this table does not include the compounds that failed before the IND (preclinical studies). So the probability for filing a NDA is even lower, if one accounts all the compounds researched by a drug maker.

The final estimate made by DiMasi et al.(2003) including cost of all failed drugs and the cost of time for making one drug is US$ 802 million. However this study was done in 2003 and costs have been rising. The latest estimate based on time adjustment and growth rates for preclinical and clinical testing periods from the Dimasi et al.(2003) study is US$ 1,318 billion[28)]. In an earlier study done by DiMasi et al[14)] drug development costs during 1970 and 1982 was estimated at US$ 331 million in 1990 dollars.

These costs are expected to be returned during the life cycle of the drug. In general once the drug is approved and marketed it will need some time to build up sales and achieve market share[17)]. For example, the pharmaceutical company needs to persuade the prescriber to use the

product[17]. Once the drug has been accepted into the market it enters the maturity period and reaches its pinnacle of sales and profits (see figure 3). After its patent expires, sales rapidly decline due to generic competition.
The bold line in figure 3 reflects the lifecycle of a drug with no competition. The dotted line reflex the life cycle when the drug experiences competition. This could be a drug that is based on another molecule (only the molecule is patented), but falls within the same therapeutic class (treats the same conditions) [17].

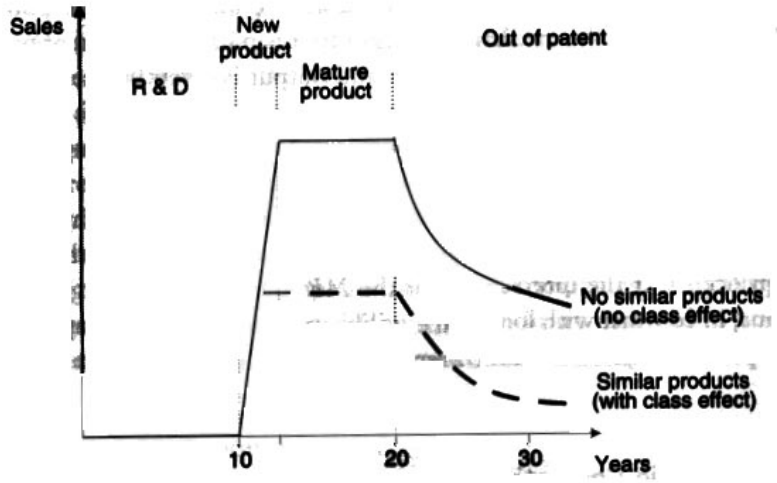


Figure 3, General life cycle of a drug, Source; S. Morris et al. Economic Analysis in Health Care, 2007

3. Generic Drugs

3.1. Generic entry

The pharmaceutical industry may belong to one of the most profitable, but is it also comes with high risks. Almost 70% of the new candidates fail[14] and only two of ten marketed drugs ever return revenues that match or exceed R&D costs[30]. As a manufacturer it would be most desirable having no competition at all to recoup investments as soon as possible.
A drug maker can patent a NCE so it has market exclusivity and no competition, but that does not last forever. The NCE is typically patented when clinical studies begin. Patents filed after 1995 expire after 20 years, leaving about 12.5 years (20 years minus 90.3 months) for the drug maker to profit as much as possible. Patents filed before 1995 expire after 17 years.

More relevant for this time period is an earlier study by DiMasi et al. (1991) that estimated to bring a drug to the market would exceed 8 years[16], leaving 9 years to earn back its investment. The difference in development time can be explained by the much shorter FDA approval times with the implementation of the Prescription Drug Use Fee Act of 1992[14]. However there is a provision enclosed in the Hatch-Waxman which states that new drugs are eligible for an extension in patent life equal to the sum of the NDA regulatory review time plus one-half of the IND testing time[20].

The other side of no competition is that the drug maker could set its price too high, thus unnecessary increasing healthcare cost. The most threatening competition in the pharmaceutical industry consists of generic firms. A generic firm takes a drug containing the same active ingredient as the brand-name to market, but cuts the price in half[6].

Consumers and politician desire the lowest price possible, as it would reduce the healthcare cost, but lower price generate less revenue and provides less incentive for drug makers to innovate.

The Hatch-Waxman Act of 1984 was a key event which aspired to create a balance between incentives for drug development and generic competition[20]. The outcome of this act reduced the cost and approval times for generics, thus allowing a faster entry to the market, but provided benefit for innovative drug makers by extending the patent life for three years under certain conditions[20].

Before the Hatch-Waxman Act was passed, generics could not entrust the same data from the brand-name drugs introduced after 1962 to establish the efficacy and safety of their own (generic) drug. Unless this would be published in scientific literature, this data was of course highly confidential and was published rarely[20].

Generic manufacturers had to withstand almost the same journey of testing as the brand-name drug to prove the safety and efficacy upon approval from the FDA. In this period many of the high selling drugs that lost its patent protection had no generic competition. In a study by Vernon and Grabowski[20] early 1986 of 200 off patent drugs, they found that only one-third had generic competition.

The Hatch-Waxman Act made it much easier for generics. Under this Act an Abbreviated New Drug Application (ANDA) was established. Generics now had to prove that their drug was bioequivalent to the brand-name drug[20]. This meant that the generic drug maker was allowed to rely on the data of the safety and efficacy from the brand-name drug that was submitted as part of the original NDA. However the Hatch-Waxman allowed the branded firm

five year data exclusivity, meaning an ANDA submitted within five years of FDA may not rely on the safety and efficacy data of the innovating firm[20].

Criteria generics must meet are dosage form, safety, strength, route of administration, quality, performance characteristics and intended use[18], but may differ in such characteristics as shape, color and packaging[20].

All generics approved by the FDA to be therapeutically equivalent are listed in the 'Orange Book', these generics may be used to substitute for brand-name drugs by pharmacists, unless the physician will not consent.

Another effect of the Hatch-Waxman Act was a faster entry of generic competitors after the innovators drug patent expired. In a study done by the US Congressional Budget (1998), they found that generic entry after expiration was one to three months. Before the Act this was three to four years.

3.2. Incentives for Generic Use

In the United States, substitution of generic drugs for brand-name drugs is regulated by law. All pharmacists are allowed to substitute drugs listed in the Orange Book, unless the physician takes specific steps to dispense as written.

States have generally two types of law for substitution of drugs: permissive substitution laws and mandatory substitution laws. In States regulated by mandatory laws pharmacists are required to substitute branded drugs for generic drugs whenever available. Permissive laws allow a pharmacist to substitute branded drugs.

According to the National Association of Board of Pharmacy's (2008)[19], 38 had permissive state laws and 14 had mandatory state laws*. Oklahoma is the only exception where it is unlawful to substitute without the authority of the prescriber or purchaser.*

Government, employers and managed care organization have hired specialized organizations called Pharmacy Benefit Managers (PBM) to manage their drug benefit programs[20]. PBMs provide their services for over half of the insured population in the US[20].

These services consist of electronic claims processing, provide a network of retail pharmacies and mail order pharmacies, and offer pharmacy benefit plan design with patient cost sharing[20].

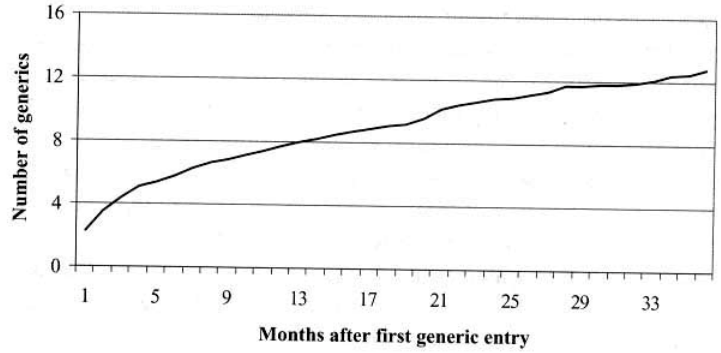
To reduce costs PMBs includes their program with strong incentives to use generic drugs if available. One of these incentives involves co-payments of patients. In one of their strict

* The US consists of 50 States, this list also includes the District of Columbia, Puerto Rico and Guam

programs patients are required to pay the full difference in price between the generic and branded drug, also known as the maximum allowable cost programs. In some cases the patient is even obliged to use the generic or will receive no reimbursement at all.
PBMs not only provide incentives to patients, but also for physicians to prescribe generic drugs. One of those incentives is the use of physician profiling. In this program a database of drug utilization is used to identify physicians who more than frequently prohibit the substitution by the pharmacist. Physicians who do not meet the norm could encounter financial penalties.
Even pharmacists have strong incentives to dispense generics, not only would they receive higher dispensing fees from PBMs, but also earn typically a higher margin, regardless whether it is paid for by a third party or paid out of pocket by the patient.
The Medicaid program, set up for individuals and families who earn a low income, was the first payer to adopt the maximum allowable cost program and in addition Medicaid has programs for automatic substitution requirements[20].
The programs to encourage generic use have been highly effective. In terms of the overall pharmaceutical market, generic products accounted for only 19% of all prescription in 1984, but this share increased to 51% in 2002[20] and in 2008 generics reached a sales share of 72%[27].

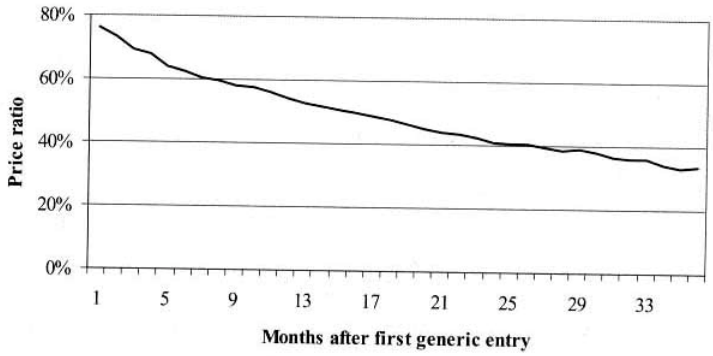
3.3. Generic Competition

The number of generic entrants after a drug patent expiration depends on how commercially successful the innovative drug is[20]. Commercial successful drugs experience not only the most competition, but the entrance of generic competitors is also comes faster when the drug patent expires[20]. Innovative drug possessing a relative big market share also encounter more price competition. The more generic entrants and more intense degree of price competition, the faster market share of brand name drug deteriorates[20].



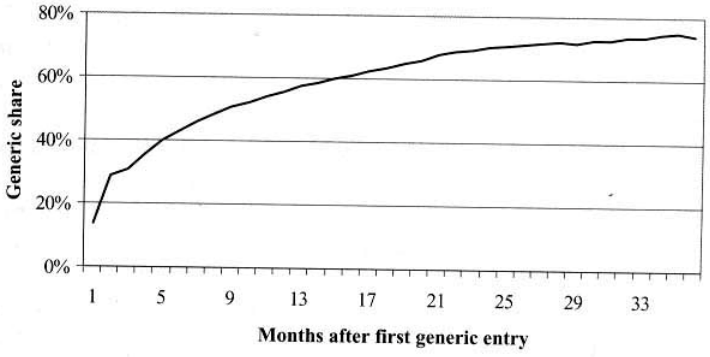
Average number of generic drug manufacturers.

Figure 3a, Source; Saha et al. (2006)



Average generic-to-brand price ratio.

Figure 3b, Source; Saha et al. (2006)



Average generic share in gram sales.

Figure 3c, Source; Saha et al. (2006)

These effects of new entrants, price and market share are shown in the figures above.
Figure 3a illustrates the time between expiration of a drug patent and the number of generic entrants. This shows how fast competition grows and after one year the innovative drug faces the competition of eight generic entrants.
Competition usually has an effect on pricing, this is presented in figure 3b. After one year the price of generics is almost half of brand name drugs, accompanied by an increasing generic market share. After one year generics gain more than 50% market share as shown in figure 3c. Grabowki did a study in 2004[20] of three top selling drugs to demonstrate how fast generics gain market share in case of successful brand name drugs. These products are Vasotec (enalapril), Zestril/Prinivil (lisinopril) and Prozac (fluoxetine), all of which had annual sales exceeding $1 billion. The patent of these drugs expired between 2000 and 2001.
In August 2000 the generic of enalapril was launched and in just four weeks resulted in 66.4% of generic prescriptions. Generic lisinopril, acquired 84% of new prescriptions in just four weeks and generic fluoxetine acquired 74.9% of new prescriptions in four weeks. If there are as many as 20 or more competitors, prices can cut two thirds down of the branded drug and fall down to marginal costs[20].
These lower prices and fast increasing market share of generics denote more savings on prescription drugs for the purchasers. The US Congressional Budget Office (CBO 1998) estimated that purchasers of prescription drugs saved between $8 billion and $10 billion dollars in the mid-1990s[20]. The share of generic prescription drugs have grown since the mid 1990s, a more recent estimate would imply an even higher saving. These substantial savings are mostly on account of third payers, such as the PBMs, employers, government and for some consumers who pay for themselves[20].

3.4. Paragraph IV Filing

The research oriented sector (the R&D department) of the industry relies heavily on the patent system[7], without a patent protection system generics could put a therapeutic equivalent drug on the market at the same moment the innovative company would introduce the drug to the market. After a year generics would seize half the market share and the branded company wouldn't have the (at least) 9 years head start to earn back its investments. In that case I do not believe innovative companies would have enough motivation to innovate, as this would not be rewarded. In the pursuit of consumers and regulators to minimize health care costs as

far as generics can help to achieve this target, while still provide enough incentives to innovate, the Hatch Waxman Act attempted to create a balance. Another important chapter of the Hatch-Waxman Act includes a marketing exclusivity period that rewards generic firms for successfully challenging a patent in court on the basis of invalidity or non-infringement[20]. To set this process in motion, a generic manufacturer files an ANDA with the FDA to claim the patent is non-infringed (Paragraph IV filing) or is invalid. The branded manufacturer has 45 days to file an infringement suit and if they choose to file an infringement suit, the approval of the ANDA may be barred up to 30 months. This provides the patent holder an incentive to litigate. The first generic to file and triumph the patent challenge is granted a 180-day marketing exclusivity[20].

One concern was the practice of listing several new patents late in the product lifecycle in an effort to provoke successive 30-months stays to delay generic competition[20]. To prevent this, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 limited each branded product to one 30-month stay[23].

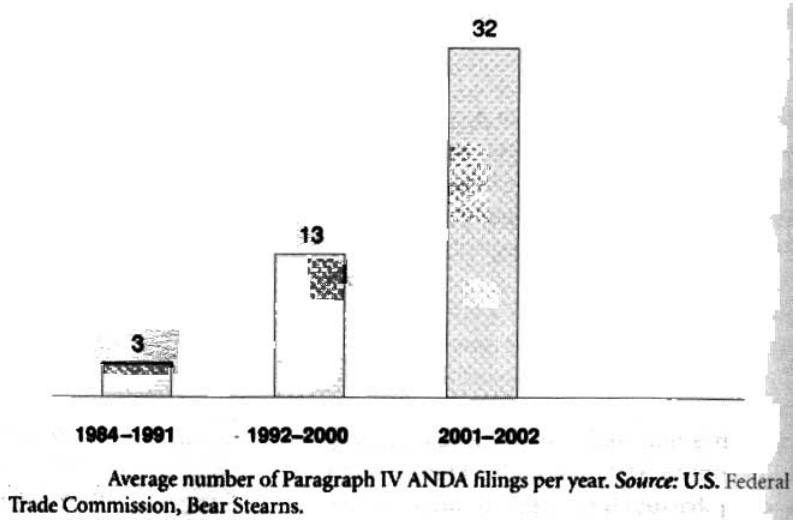
Another concern was that in some cases the first generic firm who succeeded in a Paragraph IV entered an agreement whereby the innovative firm offered a compensation for not entering the market[20]. However such an agreement would delay price competition and the payers would be the losers. This practice is also further constrained under the Medicare Prescription Drug Act[20].

The payoff for successfully challenging a blockbuster drug[†] is substantial[20] and only the first generic firm who succeeds in a Paragraph IV filing is granted the 180-day exclusivity. This is another huge incentive for generic firms to litigate and obtain the 180-day exclusivity for commercial successful drugs. In this 180-day period the generic firm can price their drug slightly below the branded drug and seize the market share of the branded drug. The additional profit can be enormous in case of a blockbuster drug[24]. An example of a successful challenge is Barr, a generic of the blockbuster drug Prozac. Before the patent challenge Barr reported product sales of $142 million and a gross margin of $24 million, leaving a gross margin profit of 16.8%[24]. After Barr enjoyed generic market exclusivity product sales increased to $360 million, with a gross margin of $103.9 million leaving a gross profit margin of 28.7%[24]. Successfully challenging Prozac nearly doubled their gross profit margin.

Generic firms may file a Paragraph IV suit four years after approval of the NCE in recognition of the five year data exclusivity. Generic marketing can begin as soon as the

[†] A blockbuster drug generates one million dollar or more revenues each year

courts have resolved the suits or when the 30-month period has expired[20], creating an exclusivity time frame for the branded firm between 5 and 7.5 years (5 years + 30 months). As shown in figure 4 Paragraph IV filings have increased from 3 per year in 1984-1991 to 32 per year in 2001-2002. If a substantial number of Paragraph IV filings are won by generic firms, there would likely be significant adverse effects on the long term expectations regarding R&D returns and can cause firms to abandon future R&D projects with uncertain patent challenge outcomes[20].



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

Figure 4

The exclusivity period of five years was to motivate innovative firms who were faced with almost no patent life left[20]. However this period may not be enough to sustain a high level of R&D activity in the US, as development costs have doubled since the Hatch-Waxman was enacted and at the same time generic competition has intensified[20]. According to Grabowski[20] the five-year period is insufficient for most new drugs to recoup the upfront R&D costs and earn a positive return on the investment.

3.5. Incremental Improvements over Branded Drugs by Generics

Pharmaceutical companies may have less capital to put in the R&D department due to generic entry, but improvement from generics is also possible. Branded and generic drugs in the same therapeutic class can differ in their side effects and efficacy profiles, adverse drug reactions, drug-drug interactions, dosing schedules and delivery systems[22]. It is also known that therapeutic responses to different drugs in a class can vary by individual, having more options

is advantageous for finding the optimal individual choice. There is also what might be called a 'system benefit' to follow-on drug development[22]. Incremental innovations lead to a stream of improvements that over time can yield substantial benefits[22]. The social value of the cumulative effects of incremental innovations can greatly exceed those of the original breakthroughs[22]. Although this might not be innovation in sense of developing a completely new compound, generics can have an added social value. Ultimately innovation in the pharmaceutical industry as the public would want it is to improve the life and health standards, and generics also play a role towards that goal.

4. Drug Life Cycle Extension

4.1. Branded Pharmaceutical Company Strategies

Third party payers and eventually we as consumers might be thankful for an increasing usage of generics as this would save us a substantial amount of money. Even law provides incentives for more generic competition and the prescription of generics.
Now assume the money saved in the mid-1990s would be entirely devoted to innovation and the development of new drugs, take into account that at least $8 billion was saved and the cost of a drug is $800 million. A very simple calculation would result into 10 NCE's that could have been developed. From 1970 to 1990 there were 10 to 25 NCE's each year[9], the 10 additional NCE's would mean a significant increase. This is another side of the coin, a conservative estimate with these numbers would suggest that in a decade 20 NCE's are not discovered of which 5 could be major[‡].
According to Grabowski[20] if there are 20 or more generic competitors, prices of generics can fall down to marginal cost. If an innovative manufacturer had only one drug and would follow the same strategy as the generic competitors to cut prices down to marginal costs, the innovative manufacturer would also have marginal revenues. In the worst case the innovator cannot attempt the risk to innovate as this thesis explained that the road to a successful NCE is a highly risky business. This scenario is of course in a theoretical simplified world and only a

[‡] This number is based on figure 1 from F.M. Scherer (2000), *The Pharmaceutical Industry*. In 1990 there were 25 NCE's of which 5 were important. However Scherer does not define an important NCE, I assume an important NCE would improve the life of more than a million people.

part of the $8 billion would be used for R&D. The scenario is to provide an example how too much stimulation of generics and passive response of innovators may have a considerable impact on innovation.

In this chapter I want to provide examples of how innovators can counter the declining revenues as a result of generic competition so a part could be put in R&D, thus fostering innovation. The strategies are based on a paper by Chandon[21].

To divest is a possible strategy[21]. The moment a drug looses its patent protection and faces generic competition, the manufacturer can choose to cut all promotional and research expenses and redirect the savings to drugs that still are protected by patent and to the R&D department for the development of new drugs. This strategy may even include price increases to take advantage of the most loyal costumers who choose to continue the use of the branded drug. Doctors, consumers and third party payers (such as PBM's) have a considerable influence with this strategy. If they still opt for the branded drug, due to lack of incentives or strong attachment to the brand, this strategy can deliver high profits. The profitability of this strategy also depends on the elasticity of the other still-patented protected drugs to the additional promotional investments[21]. If the additional investments in the patented drugs are greater than the increase in sales of the patented drugs, this strategy would not be very profitable.

A drug manufacturer could also innovate. It's not necessary to introduce a completely new NCE to innovate, drug makers can innovate by launching new forms and dosages or by demonstrating effectiveness for new indications[21]. They can also innovate by offering higher quality services for doctors and on the brand through higher promotion by the medical representatives[21]. In the United States under the Hatch-Waxman act, a new formulation involving additional trials may benefit from a three year exclusivity period[20]. A new delivery system or formulation might be even covered by a new patent[20]. One of the most successful examples is the introduction of Procardia XL by Pfizer, this version of Procardia improved the tolerability and side effects profile associated with the active ingredient. As a result Procardia XL proved to be a greater commercial success than the original formulation[20].

Another strategy is to provide more value for money[21]. New and improved flavors or a lightly better delivery systems (such as an easier to swallow pill) can lead to additional or functional consumer benefits [21]. This strategy could increase the awareness and image of the brand, so that consumers continue to use the branded drug. However generic competitors can easily copy some of the improvements from the innovative firm (such as an improved flavor),

making this strategy having a weak impact. These changes can also be picked up as marketing gimmicks and hurt the perceived scientific integrity of the brand[21].

Pharmaceutical companies can also introduce their own generics, also called pseudo-generics or 'authorized generics'[5]. US generic firms have tried to combat pseudo-generics arguing they may deter generics from challenging pharmaceutical patents[5] (the pseudo generic is allowed to sell during the 180-day period granted after a successful paragraph IV filing). However, the FDA has been unsympathetic to this view, countering that pseudo-generics are pro-competitive[5]. Pharmaceutical companies are not accustomed to producing and marketing their own generics, being successful in both branded and generic drug is very challenging.

The innovative company can facilitate a successful generic drug introduction by licensing the drug before expiry of the patent in exchange for royalties. This generic will typically be priced higher than a 'real' generic, but will benefit from preferential access to raw material and manufacturing know-how, while hampering the entrance of other generics[21].

Producing an over-the-counter version of a drug can also be a possible action for a product about to loose its patent. However before receiving an OTC status, the pharmaceutical company is required to get a FDA approval proving the product is safe for self-medication[20]. This will typically take new clinical trials evidence, but in return the company receives a three year exclusivity period for its OTC product.

Pharmaceutical companies may choose to lower the price, to narrow the gap between the price of branded and generic drugs. Pricing the branded drug the same as the generic would make doctors, pharmacists and regulators indifferent between the two and may force the weakest generic competitor out of business, given their lower economies of scale[21]. Generics can also lower their prices to counter, which may evoke a price war that would diminish profits of both parties. Another issue is that most doctors who prescribe the drug are not aware of prices, therefore price changes should also be reported to the prescriber[21].

Pierre Chandon [21] did a study of the antibiotic Clamoxyl in France and what happened after the arrival of generic competitors when its patent expired. After reviewing the different marketing strategies on this case, he concludes that it is inevitable competition from generics will erode the profitability of the original brand. But that does not mean pharmaceutical companies should take no action against its competitors. He argues that continued investment in brand building (such as innovation), coupled with well-publicized price cuts and agreements with regulators have helped extend the life of Clamoxyl, generating substantial profits[21]. Therefore every pharmaceutical company should carefully review the different

strategies before they decide to give up on their own drug[21]. It may be even more profitable, as it was in the case of Procardia XL by Pfizer.

4.2. Portfolio Interfirm Agreements in Pharmaceutical industry

This chapter is to provide a broader view into pharmaceutical innovation. In the previous chapters it is shown how fast generics can cease the market of branded drugs after the patent expires, how government regulation favors the use of generics over branded drugs and that it is inevitable generics will erode profitability. The effective patent life after FDA approval may also be insufficient to earn back the return on investments and can cause pharmaceutical firms to drop more projects with uncertain outcomes. It does seem generics do pose a serious threat to innovation in the pharmaceutical industry, in this chapter I want to review other factors for pharmaceutical in order to assess the weight of generic entry and its threat to innovation. Marketing scholars have acknowledged an important additional driver to new product development: interfirm cooperation[25]. Typically, new product development activities are internally focused, but increased complexity and the cost of developing innovative products often require expertise the firm does not have[25]. Thus strategic alliances have emerged[25].

In many industries firms form R&D agreements to access knowledge from other firms, which may aid in innovation. Industry observers conclude that firm performance in markets such as the pharmaceutical industry is strongly determined by successful management of interfirm agreements. For example, Pfizer has assembled a large portfolio of R&D agreements and claim that these efforts will a have a positive impact on innovative output[25].

In an empirical study of interfirm agreements in the pharmaceutical indusrty by Wuyts et al.[25] a distinction is made between radical and incremental innovation. When innovations incorporate a substantial different core technology and provide substantial greater customer benefits than previous products in the industry it is called ‘radical’ innovation, when one or both of the conditions are not met it is called ‘incremental’ innovation[25].

In their findings they conclude that technological diversity positively influences both radical innovation and incremental innovation. Technological diversity refers to agreements in a firm’s portfolio which cover a diverse set of technologies and thus may facilitate the inflow of more-diverse technologies. A more technological diverse portfolio of interfirm R&D agreements strengthens a firm‘s basis for learning and lowers the risk to miss the most recent

technological developments. A technologically diverse portfolio also improves the number of new product development opportunities and there is less risk to be constrained by inferior technologies[25].

Wuyts et al.(2004) also found that repeated partnering enhances radical innovation, but its effect on incremental innovation is not significant. Repeated partnering refers to in how far a firm engages in different R&D agreements with partners, which may enable the transfer for more complex knowledge. Another finding is that R&D expenses are also positive and significant related to both radical and incremental innovation, but firm size has no significant effect in any of the two innovation equations.

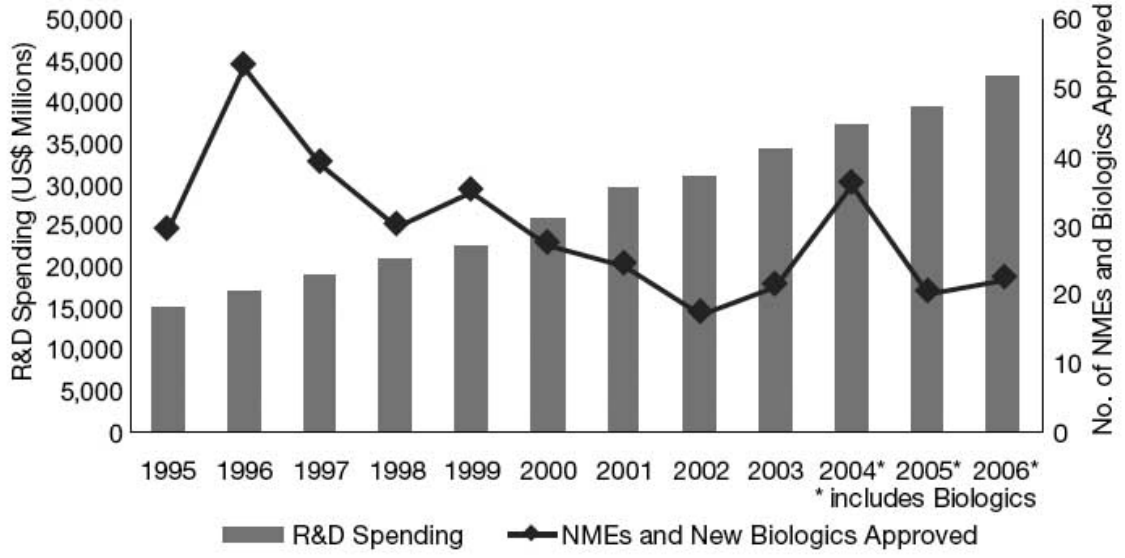
In their study they found a negative effect of technological diversity on profitability, which indicates pharmaceutical firms have difficulties recouping the high initial investment costs required for a technologically diverse portfolio[25].

Repeated partnering also has an effect on profitability[25]. Cooperation with the same partner can be cheaper than cooperation with a new partner. Partnering with the same partner can be cost-efficient because previous qualification efforts reduce the need for new qualification and monitoring practices[25]. Firms are able to assess the capability of its partner when choosing the same partner, thus reducing the risk of contracting the wrong partner because the partner was not capable of what it claims to be. This may represent a substantial saving in time and money[25]. However cooperating with the same partner too frequently may result in more attention for relationship maintenance and loyalty, than for the economic outcomes of cooperation[25]. As a result too high levels of repeated partnering can cause a decline in profitability. Wuyts et al(2004) found a strong significant effect in support of the frequency of repeated partnering. Low levels of repeated partnering require substantial partner qualification cost, whereas high levels of repeated partnering restrict economically optimal behavior[25]. The optimum lies at medium levels of repeated partnering[25].

5. Current Situation

5.1. Current Situation of the Pharmaceutical Industry

As shown in table 1 at the beginning of this thesis, sales have grown over the past years. However growth has been declining, it does seem the pharmaceutical industry is experiencing some difficulty. The member companies of the Pharmaceutical Research and Manufacturers of America (PhRMA) spent an estimated $43 billion in 2006 in the R&D department, while other non members companies spent $12.2 billion[26]. Since 1996, NME's (new molecular entities, these includes approved biologics) have been declining and from 2001 FDA approvals have been relative steady with the exception of 2004. In 1996 there were 53 approvals whereas in 2006 only 22 while R&D expenditures have more than doubled (see figure 5). According to the US Congress Budget Office most costs developing a new drug a not from the initial discovery research, but from clinical testing and regulatory approval[27].



Sources: FDA/CDER Data, PhRMA data, PricewaterhouseCoopers analysis
Note: Data on R&D spending for non-PhRMA companies are not included here, because they are not available for all 11 years

Figure 5

Between 1995 and 2005, the percentage of total corporate spending of R&D rose from 15% to 17.1%, while the percentage accounted for by sales rose from 28.7 to 33.1%[26]. Sales and marketing is by far the biggest corporate expense.

In recent years, the R&D process has become more complex. Clinical trials in particular have become more complicated, such as recruiting and retaining volunteers and the study of more complex diseases[27]. The effect of these changes is summarized in figure 6.

Increasing Complexity of Clinical Trials

	1999	2005	Percentage change
Unique Procedures per Trial Protocol (Median)	24	35	46%
Total Procedures per Trial Protocol (Median)	96	158	65%
Clinical Trial Staff Work Burden (Measured in Work-effort Units)	21	35	67%
Length of Clinical Trial (Days)	460	780	70%
Clinical Trial Participant Enrollment Rate	75%	59%	-21%
Clinical Trial Participant Retention Rate	69%	48%	-30%

Definitions:
Procedures: Including lab and blood work, routine exams, x-rays and imaging, questionnaires and subjective assessments, invasive procedures, heart assessments, etc.
Protocol: The clinical trial design plan
Enrollment rate: The percentage of volunteers meeting the increasing number of protocol eligibility criteria (percentage screened who were then enrolled)
Retention rates: The percentage of volunteers enrolled who then completed the study; declining retention rates mean firms must enroll more patients initially and/or recruit more patients during the trial

SOURCE: Tufts Center for the Study of Drug Development, "Growing Protocol Design Complexity Stresses Investigators, Volunteers," *Impact Report* 10, no. 1 (January/February 2008).

Figure 6

Most pharmaceutical firms use internal valuation mechanisms to assess the clinical and commercial potential of the compounds in their pipeline[26] and only select the ones which they perceive to have the highest probability to financially succeed. Many firms try to minimize risk by 'playing safe'[26]. When a pharmaceutical firm starts developing a new drug, they do not know whether it will be eligible for reimbursement if it reaches the market, unless it addresses a disease for which there is no existing treatment or looks likely to prove much better than any comparable therapies[26]. The Centre for Medicines Research International reported that in 2004, more than 20% of the money of the 10 largest pharmaceutical companies invested in R&D went on line extensions and other work, as distinct from new development projects[26]. In smaller companies, the percentage was over 40%[26]. The lack of R&D productivity has contributed to the decline in growth.

The US Government Accountability Office (GOA)[26] has brought up the subject of patent life. At this moment all patent last 20 years, but when the pharmaceutical product hits the market approximately half of the patent life is left to recoup investments. The GOA mooted the idea

for patent extension for truly innovative products, the pharmaceutical companies would hereby have direct incentive to become more innovative. PriceWaterCouperhouse (PWC) estimates that an extra five years of patent life would increase the cash flows from a truly innovative medicine by between 50% and 100%, depending on how vulnerable it is to generic erosion.

5.2. Future Innovation in Biotech?

This thesis is primarily based on the pharmaceutical industry, therefore this chapter will be very brief on the subject of biotechnology. However the importance of biotechnology may not be overlooked in the pursuit of innovation and the competition against generics. Biotechnology partnering may substantially aid the R&D productivity of pharmaceutical companies. For example many of the new cancer therapy projects are biologics, which are harder to copy[26)]. The pricing difference between a branded and the biologic generic product is therefore likely to be smaller than that of between a branded and generic pharmaceutical version[26)]. Products based on biotechnology are less likely to erode revenues due to generic entry. Biologics aid to sustain a higher level of revenues after patent expiry, this may help to increase R&D productivity.

Conclusion

Generic usage has increased substantial over the last years. PBMs provide services for over half of the insured population in the US and use programs to encourage generic products which are highly effective. Not only specialized organizations favor generic products, but also regulations have been made to prescribe generics whereas possible and to allow easier entry for generic competition. As the share of generics increases and the share of branded drugs quickly deteriorates after patent expiry, most profits of branded drugs must be made within the period of patent protection, in order to recoup the drug development investments.
The Hatch-Waxman Act was to provide balance between generic competition and incentives for branded firms to innovate. The Hatch-Waxman Act does offer extension of patent life under certain criteria and 5 year data exclusivity for innovative drugs, but the Act was passed in 1984 and does not recognize the increased complexity and cost of drug development. Estimated drug development costs have increased close to 300%[§] since 1987, but branded drugs still receive the same patent protection period to recoup investments. Non-infringement suits haven't made it any easier for innovative firms. Such a Paragraph IV filing may delay entry of generic competition up to 30 months, but the payoff for successfully challenging a drug might be substantial. As a result numbers of Paragraph IV filings have grown, innovative firms now have to decide which future R&D projects have the best odds to withstand non-infringements suits regarding R&D returns. Projects with the lowest probabilities might be dropped, which does not improve R&D productivity.
There are various strategies available to extend the product lifecycle, which might prove successful and interfirms agreements can be made to improve innovation, however these are not enough to sustain a high level of R&D activity. If the patent period for branded drugs is extended by law, revenues will increase. These extra revenues make it possible to invest in the R&D department, thus make more innovation possible. But current regulations cause R&D expenditure not to be efficient, as most of the expenses are spent on the regulatory road to drug approval. This is an issue which should be addressed by the authority. However, a more efficient new drug approval process might increase the probability of unsafe drugs.
Generics are the root of declined revenues and drug development has become more complex and costly. At the current situation, patent period is too short for branded firms to provide

[§] Estimated costs to develop a new drug were $331 for pharmaceutical firms between 1970-1987 and $1,318 billion in 2007.

incentives for innovation. If patent period would be extended more innovation is made possible. However this might result to an increase in healthcare cost.
Generics do pose a threat to innovation, but due to incremental improvements over branded drugs may aid innovation. I believe the biggest threats to innovation at this moment are the current patent protection system and the increased complexity of the drug development process.

Reference List

1) http://money.cnn.com/magazines/fortune/global500/2008/performers/industries/profits
2) http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/Global_Pharma_Sales_2001-2008_Version_2.pdf
3) http://www.cms.hhs.gov/NationalHealthExpendData/downloads/tables.pdf
4) M.A Santoro, T.M. Gorrie (2005), 'The campaign against innovation', Ethics and the Pharmaceutical Industry.
5) A. Hollis (2005), 'How do brands' "Own Generics" Affect pharmaceutical prices? ', Review of industrial organization.
6) A. Saha, H. Graboski; H. Bimbaum, P. Greenberg; O. Bizan (2006), 'Generic competition in the US pharmaceutical industry', International Journal of the Economics of Bussiness.
7) R.E Caves; M.D. Whinston, M.A. Hurwitz (1991), 'Patent Expiration, Entry, and Competition in the US Pharmaceutical industry', Brooking Papers on Economic Activity.
8) http://www.kff.org/rxdrugs/upload/3057_07.pdf
9) F.M. scherer (2000), 'The Pharmaceutical Industry', Handbook of Health Economics, Volume 1.
10) http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054819.htm
11) http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm
12) http://www.clinicaltrials.gov/ct2/info/glossary#phasel
13) http://www.abpi.org.uk/publications/pdfs/phase1_guidelines.pdf
14) J.A. Dimasi, R.W Hanson, H.G Graboski (2003), 'The Price of Innovation', Journal of Health Economics.
15) http://molinterv.aspetjournals.org/cgi/reprint/2/1/6
16) F.M. Scherer (1993), 'Pricing, Profits, and Technological Progress in the Pharmaceutical Industry', Journal of Economic Perspectives.
17) S. Morris; N. Devlin; D.Parkin (2007), 'Economic Analysis in Health Care'.
18) http://www.fda.gov/Drugs/ResourcesForYou/ucm167906.htm

19) https://www.ptcb.org/AM/Template.cfm?Section=Regulations&Template=/CM/ContentDisplay.cfm&ContentID=3286&FusePreview=True&WebsiteKey=9d90bd98-be45-4b90-ae8c-25ab71fa0923
20) H.G. Grabowski (2007), 'Competition between Generic and Branded Drugs', Pharmaceutical Innovation: Incentives, competition, and cost-benefit analysis in International Perspective.
21) Pierre Chandon (2003), 'Innovative Marketing Strategies after Patent Expiry: The case of GSK's antibiotic Clomaxyl in France', International Journal of Medical Marketing.
22) J.A. DiMasi and C. Paquette (2004), 'The Economics of Follow-on Drug Research and Development', Pharmacoeconomics, 22 Suppl. 2.
23) M. Padden, T. Jenkins (2004), 'Food and Drug Law: Hatch-Waxman Changes, The National Law Journal', http://www.howrey.com/docs/00503040006Howrey.pdf
24) http://www.paragraphfour.com/explained/why_challenge.html
25) S. Wuyts, S. Dutta and S. Stremersch (2004), 'Portfolios of Interfirm Agreements in Technology-Intensive Markets: Consequences for Innovation and Profitability', The Journals of Product Innovation Management.
26) PricewaterhouseCoupers (2007), 'Pharma2020: The vision'
27) PhRMA Industry Profile Report 2009, http://www.phrma.org/files/PhRMA%202009%20Profile%20FINAL.pdf
28) J.A DiMasi and H. Grabowski (2007), The Cost of Biopharmaceutical R&D: Is Biotech Differerent, Managerial and Decision Economics.
29) J.A Dimasi, R.W. Hansen, H.G Graboski, L Lasagna (1991), 'Cost of innovation in the pharmaceutical Industry', Journal of Health Economics.
30) J. Vernon, J. Golec, J.A. DiMasi (2008), Drug Development Costs when Financial Risk is Measured Using the Fama-French Three Factor Model', unpublished working paper (reference obtained from PhRMA Industry Profile Report 2009).