The Evaluation of System-Wide Financial Incentives in Pipeline Decisions in The Pharmaceutical and Biotechnology Industry: The Paradox of R&D Spend Vs. New Drug Approvals

By

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ABSTRACT

For several decades, the ascendency of the Pharma & Biotech sector was largely driven by favorable macro-economic conditions combined with an astonishing level of innovation and a clear focus on addressing unmet medical needs. Significant R&D investments led to innovative drugs that changed clinical practice across multiple illnesses and contributed to an overall rise in life expectancy around the world.

Unfortunately, this trend has not continued. Since the mid-90s', the approval of novel drugs has plummeted despite record levels of R&D investment. It is estimated that between 2000 and 2010, the top 10 global Pharma and Biotech companies have collectively invested over $500 Billion in R&D. In the same period, only about 150 novel drugs entered the market. This is partly explained by the fact that quick-wins have been harvested, and that further progress in treating grievous illness is harder to achieve. This is compounded by increasing concerns about the long-term safety of drugs and the conservative regulatory climate that has prevailed since 2000. In this challenging regulatory and cost environment, the basic economic model of the industry is now being questioned. In this work I review the recent financial performance of ten major global pharmaceutical companies, and the challenges faced by the industry in moving from a deterministic, blockbuster era to a more stochastic era defined by multiple unknowns.

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Title: *Charles E. and Susan T. Harris Professor,* Professor of Finance

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MIT would have remained a distant dream had it not been for the undying support of my family. I owe a lifetime of gratitude to my "angels" Dhruv, Chirag, Sumathi, Rajam, Nirmala, Ravi, Chikki, and my mother Prema, for making this possible. My wife Sumathi is my ultimate role model – the epitome of love, support, loyalty and hard work. The untold sacrifices that each of them made is beyond compare. I am the luckiest person alive to have them in my life.

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Chapter 1

Introduction

The relentless increase in healthcare costs in the US stands in sharp contrast to measurable outcomes in the overall health of our population. On a per-capita expenditure basis, Americans should be disease-free and living forever! At nearly 18% of GDP, healthcare spending has become a clear and present danger to the US economy, and by extension, the ability of the US to compete in a rapidly evolving global landscape. Resolving the healthcare crisis in the US has become one of the key issues of our time, and the intense interest generated by the recent debate in the United Sates Supreme Court in its consideration of the Affordable Care Act of 2011 is indicative of the essential importance of this issue. More broadly, the economic, social, and moral implications of access to healthcare play an important role in every region of the World.

Much has been written in recent literature about the dramatic impact of the rising cost of healthcare. However, there is little consensus on why the costs continue to increase, let alone any potential solutions that may be on the horizon. Vested interests often find creative ways to deflect the cost discussion, choosing instead to diffuse public debate by implicating the opaque nature of the system, and the misalignment of the interests of the various participants in the healthcare system. These participants include patients and consumers of healthcare on the one hand, and an extensive set of "providers", "payers" and "regulators" on the other hand.

In its purest form, the demand for healthcare services is met by a supply of such services by a range of providers. Established economic and finance theory would suggest that in an environment with visible demand and competent suppliers who can meet that demand, market forces should prevail. If as in other sectors of the economy, market forces did prevail in healthcare; those patients and consumers of healthcare services who can participate in the market would benefit from the theoretical efficiency of the market, and would get the best available services at "market" prices. Competition would drive innovation, and those suppliers who cannot sustain their competitive edge over time would disappear. However, the

healthcare market is not efficient. Leading economists have challenged the broader notion of market efficiency, and have made compelling arguments that suggest that market efficiency is at best fleeting, and flawed.

Healthcare is not optional – every person in the world will need access to healthcare at some point in their lifetime, often multiple times. Several countries around the world have made this fact central to their healthcare policies. Most western economies have adopted some form of a single payer system in which essential services for the entire population are paid for by a central authority (e.g. the National Health Service in the United Kingdom) and provided by designated entities who provide products and services at some pre-established, and regulated price. From a macro-economic perspective this seems to work quite well in countries like Canada, The United Kingdom, France and others. Everyone has access to essential products and services, while access to non-essential or optional services is more tightly controlled, and in some cases only available to those with adequate wealth to pay for these products and services. These models of healthcare delivery have been in existence for some time and have been extensively studied, and will not be the focus of this work.

The Pharmaceutical Industry

The value of the global pharmaceutical market in 2013 is estimated to exceed $975 billion, and is expected to grow at 4 - 6 percent on a constant dollar basis. This forecast is provided by IMS Health, a leading provider of aggregated data for the healthcare industry, and it predicts global pharmaceutical market sales to grow at a 4 - 7 percent compound annual growth rate (CAGR) through 2013, and takes into account the impact of the global macroeconomic conditions, the changing mix of innovative and mature products, and the rising influence of healthcare access and funding on market demand.

In the pharmaceutical industry, nothing is quite as exciting or purposeful as building and advancing a robust, dynamic pipeline of new molecules that have the potential to address unmet medical needs. The biopharmaceutical sector in the United States is the global leader in R&D and medical innovation, with several hundred new drugs approved by the FDA in the last

decade – a resounding success by any measure. Many of these scientific breakthroughs led to dramatic improvements in the overall health of people around the world. The success and productivity of their pipelines drove significant financial returns to their shareholders, and spurred additional investments in R&D. It is estimated that in 2011, the biopharmaceutical sector in the United States invested over $100 billion in R&D, with nearly 3000 compounds being studied across a range of diseases.

Table 1.1. Drugs under development in 2011 by major diseases. (*Source: Adis R&D Insight Database and PhRMA*).

Condition	Number of Medicines in Development
Alzheimer's and Other Dementias	98
Arthritis	74
Cancer	878
Breast Cancer	125
Colorectal Cancer	82
Lung Cancer	120
Leukemia	119
Skin Cancer	86

Condition	Number of Medicines in Development
Cardiovascular Disorders	237
Diabetes Mellitus	193
HIV/AIDS	81
Mental and Behavioral Disorders	252
Parkinson's Disease	25
Respiratory Disorders	334
Rare Diseases[2]	303

Source: Adis R&D Insight Database and PhRMA[1]

The impact of these R&D efforts is felt around the world. Life expectancy in most regions of the world is at an all-time high. Diseases once considered incurable and life-ending have been converted into chronic conditions that can be effectively managed with medications. Chronic conditions that once drained productivity are now controlled with medications such that most people with these ailments can contribute more effectively to the economy and society at large.

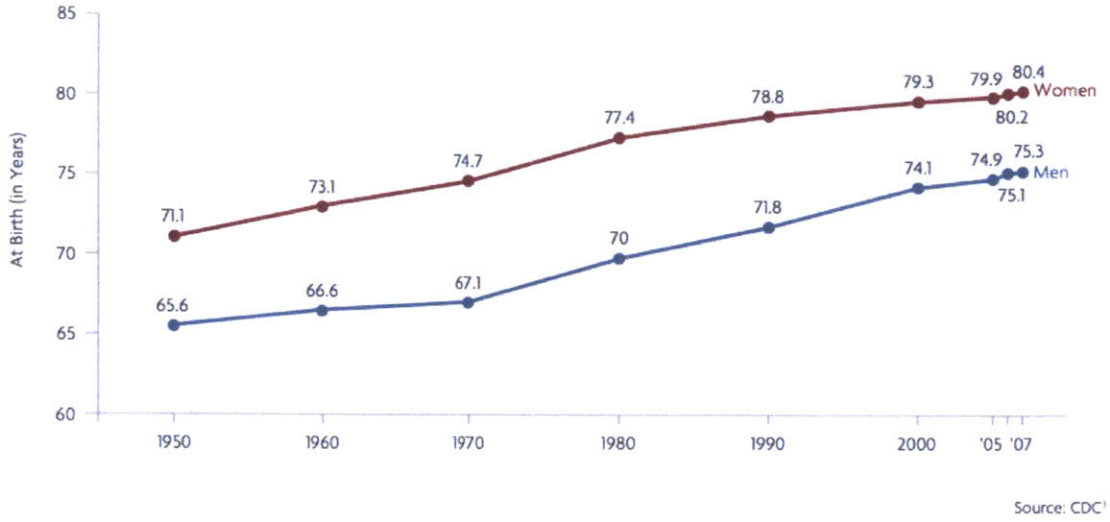


Fig. 1.1. Life expectancy at birth (in years) in the United States (*Source: Centers for Disease Control (CDC), USA).*

Patients suffering from heart disease, many types of cancers, HIV/AIDS, diabetes, and many other illnesses have seen dramatic improvements in their health, productivity, and quality of life. In the US alone, the economic burden of chronic illnesses is enormous. Published figures estimate the annual economic cost to the US economy at over $250 billion from heart disease, diabetes, and cancer alone. The discovery of effective medicines for these indications has been an important factor in the overall improvement in the outlook for these patients, many of whom now live more productive lives.

These improvements in the overall health of the population do come at a cost. Prescription drugs make up about 12% of the overall cost of healthcare in the United States, or about 2% of GDP. About 40% of this is tax financed through programs such as Medicare and Medicaid. Another 40% is financed through insurance, with the remaining 20% being funded directly by patients. The recent debate on the unsustainability of healthcare costs has brought the cost of prescription drugs into sharp focus. The biopharmaceutical industry is now faced with a substantial challenge of demonstrating that innovative drugs can truly provide differentiated benefit to patients – benefits that significantly outweigh costs. For people with serious illnesses, this debate is very meaningful.

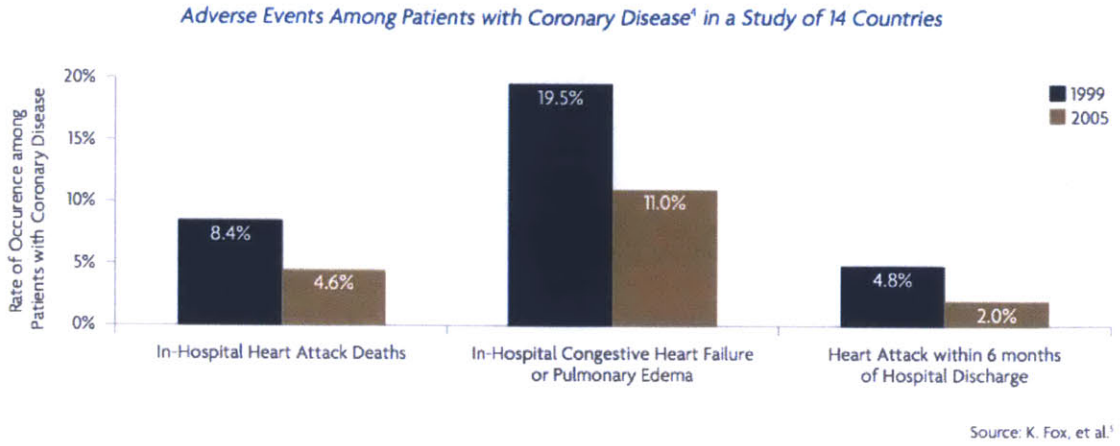


Fig. 1.2. Impact of CV medicines in reducing Adverse Events in Cardiac patients. (*Source: PhRMA)*

Even today, the term "cancer" still strikes fear in those who are diagnosed with this dreaded disease. However, significant progress has been made in improving our understanding the complex world of oncology. Improved diagnostic methods which can help with early detection combined with better, more targeted drugs have contributed to major gains in combating some specific types of cancers such as breast cancer and prostate cancer. Despite these advances, we are a long way from declaring victory over cancer. Cancer biology is complex, and progress in understanding the fundamental aspects of this disease is takes time. Progress is slow, and much more work remains to be done before most forms of cancer are either prevented or effectively treated.

The biopharmaceutical industry has built effective partnerships with publically funded R&D organizations such as the National Institutes of Health, and academic institutions to bring advances in cancer biology to the clinic. These collaborations have produced stunning results in many areas of oncology, and have benefitted millions of people around the world. However, these productive collaborations have recently come under pressure due to budgetary constraints, and could slow the progress of translating basic research into drugs that can benefit patients.

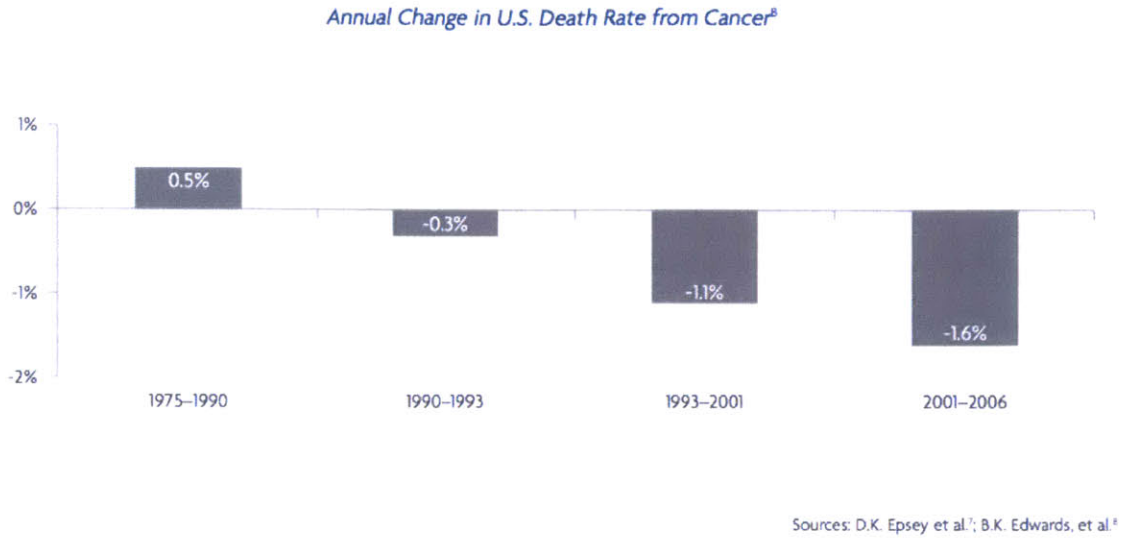


Fig. 1.3. Annual reduction in cancer deaths in the US, 1975 – 2006. (*Source: D.K Epsey et al; B.K. Edwards et al; PhRMA).*

In addition to the progress being made in treating conditions such as heart disease and cancer, breakthroughs in less common conditions have resulted from R&D efforts from many innovative companies. Between 1997 and 2010, more than 200 new drugs were approved for the treatment of rare diseases. In the United States, the term "rare disease" has a specific regulatory meaning and refers to those diseases that affect less than 200,000 people. It is noteworthy that until recently, for most patients suffering a rare disease there were no treatment options.

The significant increase in the R&D efforts directed towards rare diseases is a good example of the collaborative effort by the biopharmaceutical industry, academia, and the FDA. The FDA Office of Orphan Products Development (OOPD) was set up with the express purpose of advancing the evaluation and development of products for the diagnosis and treatment of rare diseases. Initially, those companies engaged in addressing the needs of patients with rare diseases were not expected to recover their R&D and marketing costs, and the FDA provided incentives such as accelerated review for other, non-orphan submissions from these

companies. More recently, orphan drugs have proven to be immensely profitable. This is shift towards obtaining an orphan designation, particularly in oncology, is significant.

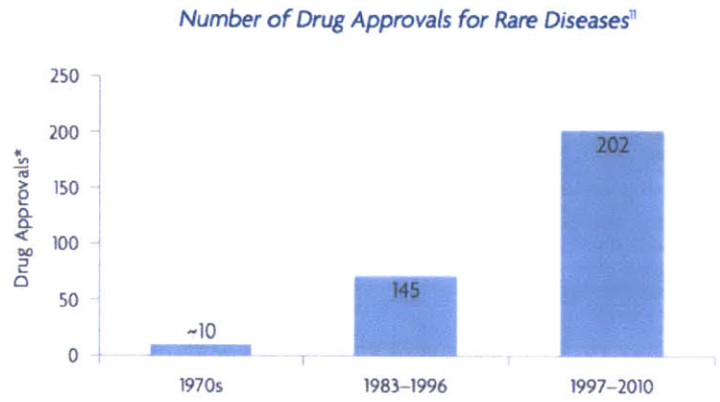


Fig. 1.4. Number of drug approvals for Rare Diseases, 1970s – 2010. (*Source: US FDA)*

There is little doubt that the biopharmaceutical industry's commitment to R&D and innovation has a direct and measurable benefit to patients, and has played a role in controlling overall healthcare costs. In the case of a chronic illness like diabetes, there is direct evidence from the experience of clinicians and payers that there is a nearly 50% reduction in annual healthcare costs for patients taking an effective diabetes drug.

This is indicative of the fact that in the United States, the biopharmaceutical industry is one of the most R&D-intensive sectors of the economy. Most large companies in this sector routinely invest between 15% and 25% of annual revenue in R&D. This level of investment was seen as fundamental to the survival and future growth of the industry, and was rewarded by investors, who more often than not viewed a thriving pipeline as a positive indicator of future earnings.

Much of this has changed. The biopharmaceutical sector is not immune to the recent economic challenges. At a time when the United States and indeed much of the world, is facing

unprecedented economic challenges, the underlying business model of the R&D intensive biopharmaceutical industry has come under increased scrutiny. This business model is defined by the significant risk and major investments in R&D that are recouped by only two of every 10 approved medicines. This is in sharp contrast to other industries where more than one in three investments in R&D and product development can yield significant financial returns.

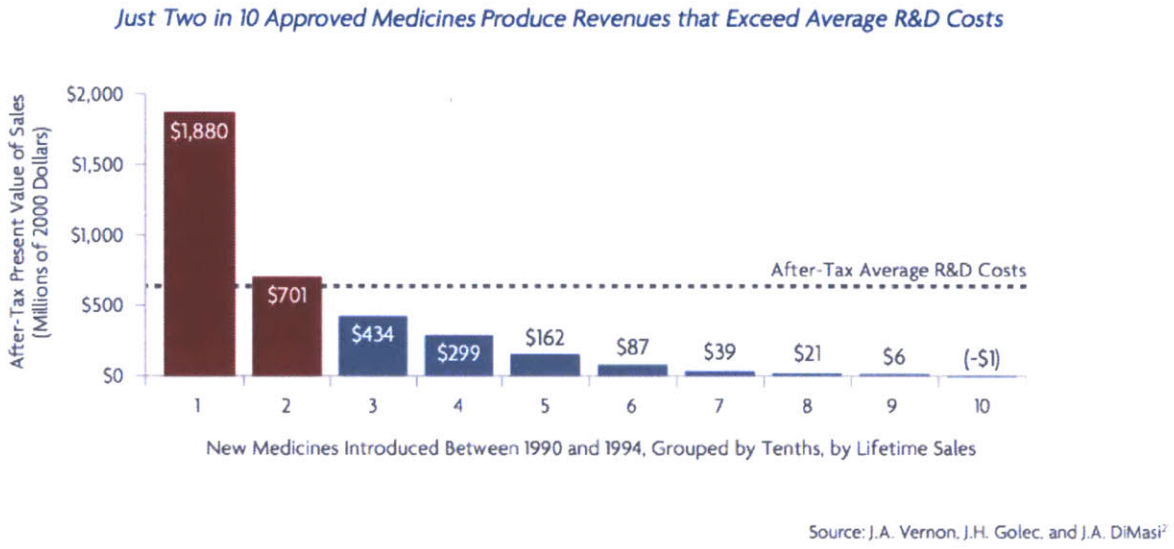


Fig. 1.5. Only two out of every 10 new drugs launched will recoup R&D costs. (*Source: J. A.DiMasi et al*)

In the face of these economic challenges, most of the biopharmaceutical companies that I studied have initiated a strategic review of the key factors that impact the industry and their companies. The less than stellar financial returns of these companies in the last few years, has led shareholders to question the underlying risk inherent to the industry.

Changes in the market dynamics, the growing influence of payers in determining the reimbursement levels for drugs, increased scrutiny from regulators, competition from emerging markets such as China and India, and changes in the intellectual property landscape are all key factors that must be addressed to restore the health of the industry.

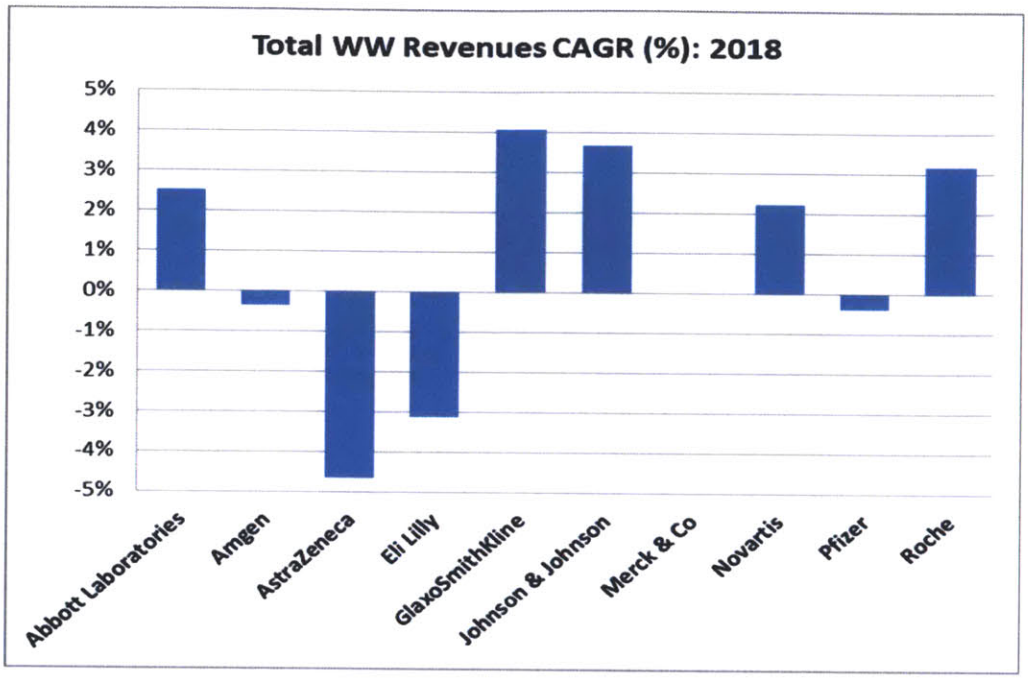


Fig. 1.6. Expected normalized growth in Net Income (CAGR) 2011 – 2018 for the companies participating in this study. (*Data Source: Evaluate Pharma*)

Table 1.2. Worldwide prescription drug sales of the companies in the study. 2011 & 2018. (*Source: Evaluate Pharma)*

Worldwide Prescription Rx Sales/ Ranking/ Market Share

Prescription (Rx) Pharmaceuticals	Data			Market Share		Market Rank	
	2011	2018▼	CAGR	2011	2018	2011	2018
Novartis	46,675	50,869	+1%	6.5%	5.8%	2	1
Pfizer	53,547	46,899	-2%	7.5%	5.3%	1	3
GlaxoSmithKline	34,972	46,000	+4%	4.9%	5.2%	6	4
Roche	37,038	44,765	+3%	5.2%	5.1%	5	5
Merck & Co	41,875	40,696	+0%	5.8%	4.6%	3	6
Johnson & Johnson	22,304	27,083	+3%	3.1%	3.1%	9	7
Abbott Laboratories	22,435	24,493	+1%	3.1%	2.8%	8	8
AstraZeneca	32,366	22,375	-5%	4.5%	2.5%	7	10
Amgen	15,295	14,800	+0%	2.1%	1.7%	13	16
Eli Lilly	20,397	13,578	-6%	2.8%	1.5%	10	17
Sum	326,904	331,558	+0%	45.7%	37.5%	-	-
Rest of Market	388,997	552,262	+5%	54.3%	62.5%	-	-
Total Market	715,902	883,820	+3%	100.0%	100.0%	-	-

Note: sum aggregations exclude data from merged companies to avoid double accounting.

Since 2000, despite significant increases in R&D spending, the number of new drugs approved by the FDA has remained about the same. Further, many of the drugs approved by the FDA failed to meet their initial sales projections.

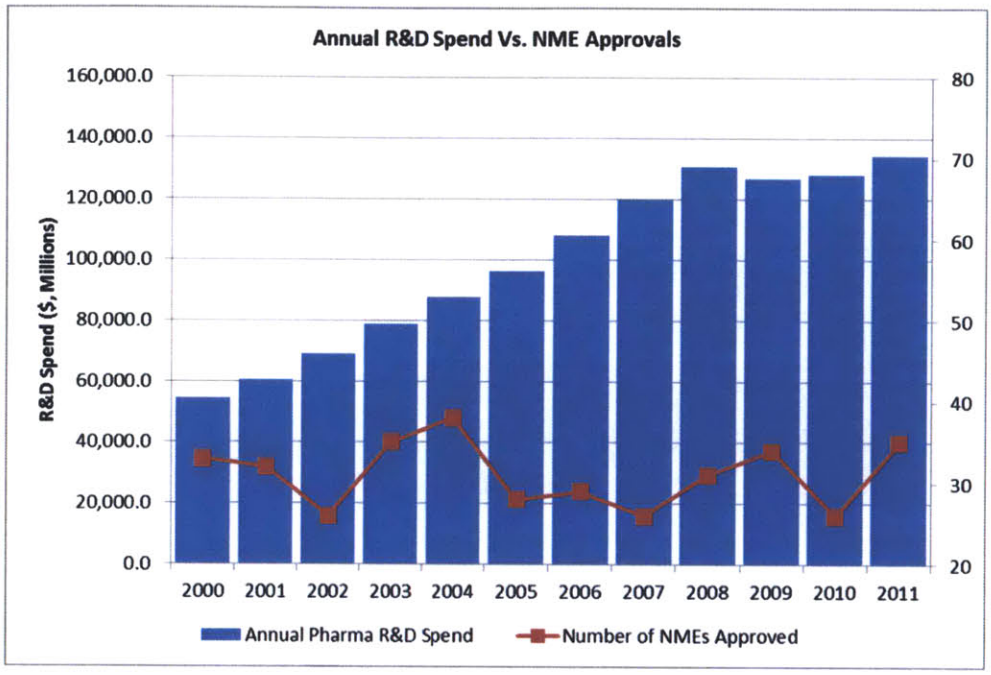


Fig. 1.7. Annual R&D spending Vs. Number of NMEs approved. *(Data Source: US FDA).*

Simultaneously, there has been a significant shift in public investment in basic R&D. Budget cuts at the NIH have led to a reduction in the amount of R&D spending in basic biology, thus slowing the progress in understanding complex diseases. About 30% of the total annual budget in disease biology, translational research, and clinical medicine comes from the NIH in the form of grants to academia and small companies. These grants support basic science and clinical medicines, often at leading academic institutions around the United States. Many of these academic institutions are affiliated with teaching hospitals and academic medical centers (AMC) that play a crucial role in advancing the understanding of disease biology.

In chapter 2, I examine some of the key factors that impact the evolving business model of the biopharmaceutical industry, and outline the methodology that was used to obtain the background data that forms the basis of this study. In chapter 3, I examine the financial

performance of the biopharmaceutical industry and some of the factors impacting the recent performance of the industry. Finally, in chapter 4, I review some elements of the emerging business models in the industry, and suggest areas for additional study. I conclude by making a few specific recommendations that could have a positive impact on the industry in the future.

Chapter 2

Generally, any pharmaceutical, biotechnology, medical device, or diagnostic company seeking to develop, test, and market a prescription drug, device, or diagnostic test in the United States must seek FDA approval. The process of discovering, developing, and eventually bringing a new drug, device, or product into the market is time consuming and expensive, and the FDA plays a central role in the industry. It is worth noting that until recently, the FDA was the undisputed leader in the determining the scientific and medical benefits of any drug, device, or diagnostic that was on the market. The scientific and medical expertise of the agency was so strong, that often, regulatory agencies of many other countries simply followed the precedent set by the FDA in approving or rejecting any given drug, device or diagnostic for their own domestic markets.

In order to review the R&D process in the appropriate context, it is first useful to briefly review the essential process that the US FDA follows in evaluating and approving a prescription drug for use in the United States.

The Role of Regulation

Unlike most other industries, the healthcare industry is highly regulated. Regulatory bodies such as the Food and Drug Administration (FDA) in the United States, the European Medicines Agency (EMEA), and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan play a significant role in shaping the healthcare environment in their countries, and indeed around the world. These agencies were created to ensure that consumers of health services and products in their respective countries would be protected from harm. Mistakes in healthcare, whether accidental or deliberate, can lead to serious consequences for individuals and groups of people, including permanent injury, or death.

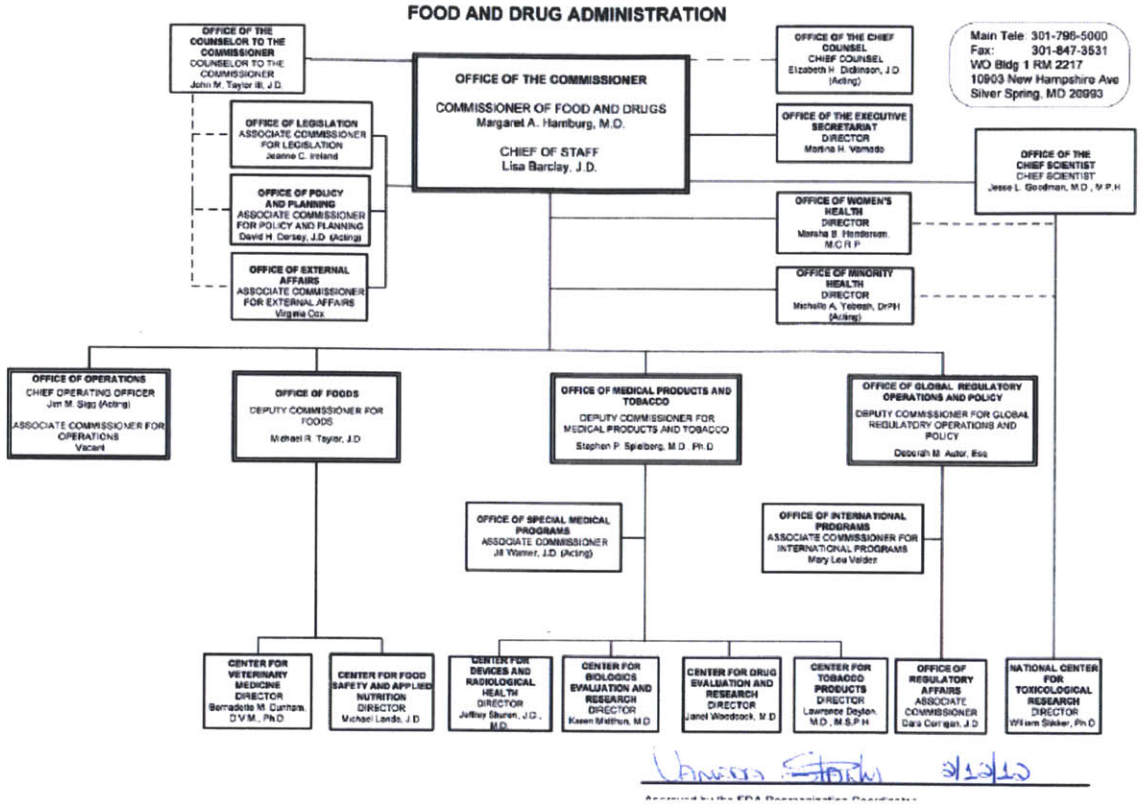


Fig. 2.1. Representative Organizational Chart of the United States Food & Drug Administration (*Source: US FDA)*

The extensive regulatory authority of the US FDA is illustrated in the organizational chart of the agency depicted in Figure 2.1. Of particular interest to the Pharmaceutical and Biotechnology industry are three organizations within the FDA – The Center for Drug Evaluation and Research (CDER), The Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). Between them, these three agencies account for 100% of the regulatory oversight for every innovative drug (small molecule or biological drug), generic drug, medical devices, and medical diagnostics that is developed, tested, and marketed in the United States.

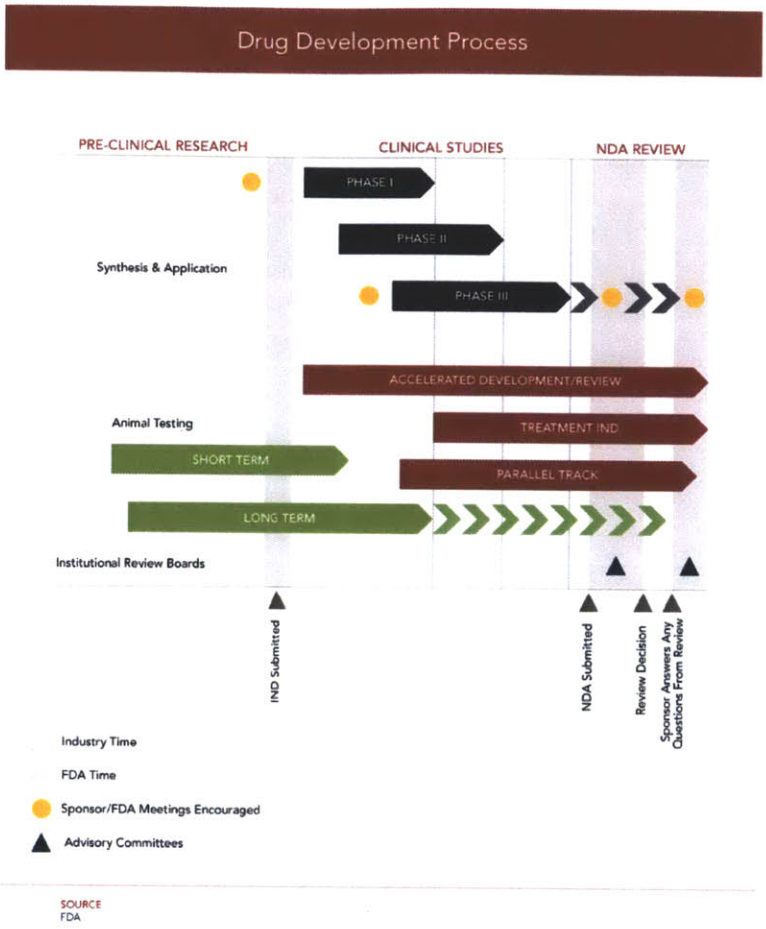


Fig. 2.2. The drug development and approval process (*Source: US FDA)*

As shown in Fig. 2.2., the discovery, clinical development and commercial launch of a therapeutic drug in the United States is overseen and regulated by the FDA. Most drugs take between 8- 12 years to go through the process.

First, the industry uses the growing understanding of biology to identify 'targets'. A target is a naturally occurring biological material (a protein, an enzyme, etc.) in the body that plays key role in the development of a disease, or the symptoms associated with that disease. The selection of the biological target is very important, since it is essential to establish a clear link between the disease of interest and the underlying biological target. Once such a target has been validated, the next step is to identify a synthetic chemical compound, natural (often

plant-derived) compound, or a biological material such as a protein or antibody that could modulate the activity of a given biological target. Since the attrition rate of such compounds at this earliest stage of the drug development is very high, technologies such as automation, robotics, informatics, high-throughput screening are employed to identify "hits" that might be suitable to progress to the next stage of the discovery process.

After the "hits" are identified, they are further tested to verify that they are indeed "valid hits" – those that demonstrate genuine activity in the biological assay that represents the activity of the disease target under study. These "validated hits" are tested in secondary biological assays to further ascertain their biological activity. Typically, only a small fraction of the initial set of hits will progress to further testing. These verified hits are termed "leads", and mark an important decision point in the early discovery process.

Almost always, these lead compounds need further improvement. Such improvement is necessary to enhance the selectivity of the compound to ensure that it acts primarily on the disease target for which it was tested. In addition, the lead optimization process is designed to ensure that desirable "drug like" properties are improved. Optimizing these drug like properties ensures that once fully developed and tested, the drug will be absorbed by the body (bioavailability), reach the desired point in the body to find the appropriate target (pharmacodynamics), remain in the body for the right duration (pharmacokinetics), have minimal side effects (off-target effects), and can be manufactured efficiently, and cost effectively. Each of these steps marks a significant commitment of resources – both people and capital. Mistakes made at this stage of the discovery process are very costly.

Once a lead compound is optimized, additional testing is performed. These tests are performed "in vitro" with living cells that are representative of the disease condition, in tissue cultures that might better represent the biological target, or "in vivo" in live animals (mice, rats, dogs, etc.). This stage of "pre-clinical" testing marks another important decision point. Any compound which does not pass the stringent safety testing that is performed at this stage will not progress into human clinical trials. A compound that successfully passes the pre-clinical

stage of testing is called a "clinical candidate", and upon further review, it will likely progress into human clinical trials.

However, before any human trials can commence, a clinical trial protocol is developed. This protocol provides a detailed definition, methods and procedures, expected outcomes, and operational parameters of the proposed clinical trial. The protocol undergoes rigorous review by an independent committee consisting of experienced independent scientific experts, practicing physicians, and researchers with expertise in the field. The committee will review the ethical standards of the clinical trial design. Difficult questions such as who gets the drug Vs. the placebo, whether children are included in the trial, how sick the patients participating in the trial will be, etc. This review process is comprehensive, and the committee has final authority on whether a trial can commence. The committee also has the authority to halt a trial for any reason that might potentially harm a patient.

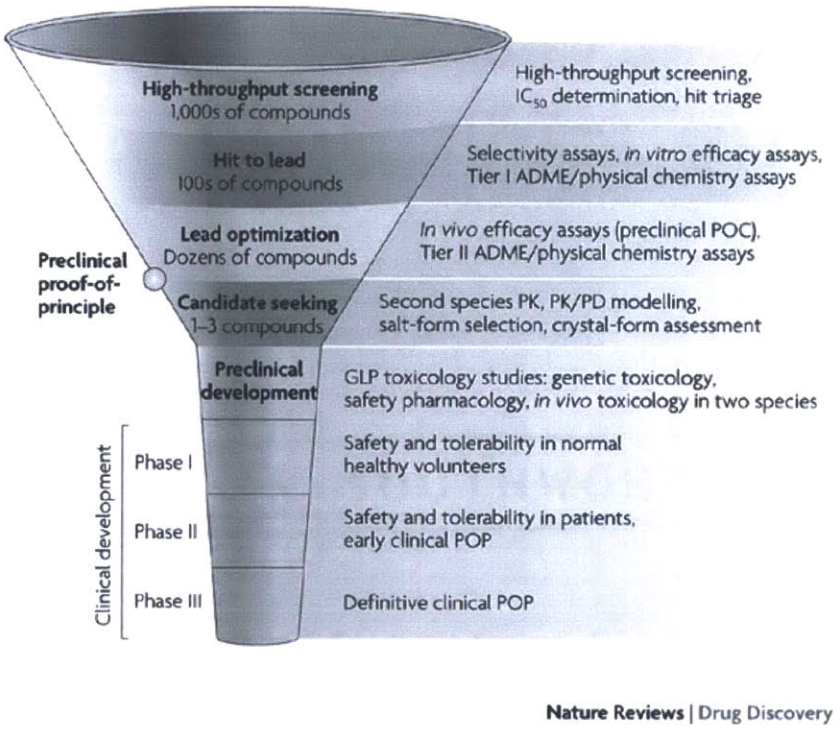


Fig. 2.3. The drug development "funnel" (Source: *Nature Reviews Drug Discovery* **6**, 636-649 (August 2007))

Upon the successful completion of pre-clinical testing, and with the approval of the appropriate review committees, clinical trials can commence. This marks a critical point in the drug development process. A significant portion of the costs of developing a new drug lies in the clinical trial phase. Of the nearly $1.5 billion that is required to successfully launch a new drug, fully 60% or more of the costs are incurred during the conduct of the clinical trials. These trials may be simple trials with a few patients at a few centers in one geographical location, or as is the case most often, these trials involve thousands of patients across dozens of centers around the globe. The safety and well-being of all clinical trial participants is of utmost importance. Typically, clinical trials are conducted in accordance with guidelines developed by the International Conference on Harmonization (ICH) and the principles contained in the World Medical Association Declaration of Helsinki on the Ethical Principles for Medical Research Involving Human Subjects (2008). Clinical trials are conducted in phases as defined below.

- **Phase I** trials are intended to confirm how the potential new drug is absorbed and distributed through the human body, and is usually conducted with a small group of healthy volunteers, except in trials involving potential treatments for certain types of cancers, where a Phase I trial may involve patients suffering from the actual illness.
- **Phase II** trials will include a larger number of patients with the condition that the proposed new drug is intended to treat. The purpose of this phase is to establish whether the drug will have the beneficial effect on the particular disease process, and what doses and methods of administration may be most appropriate.
- **Phase III** trials follow from successful outcomes from Phase II trials. This is a much larger study likely to be conducted with many hundreds (or thousands) of patients in several countries. Often, multiple Phase III studies are required to meet the regulatory burden of proof for safety and efficacy, superiority over existing treatment choices, and economic effectiveness of the new drug.

These three phases of clinical trials may last many years – often more than seven years. It is important to note that very few drug candidates actually make it all the way through the

clinical trial process successfully. For most pharmaceutical companies, the cumulative failures of compounds in clinical trials prove to be very expensive. Failures in the later stages of clinical trials (phase II and beyond) are particularly expensive and damaging. Many years of work, and hundreds of millions of dollars are lost when a drug candidate fails in the later stage s of clinical trials.

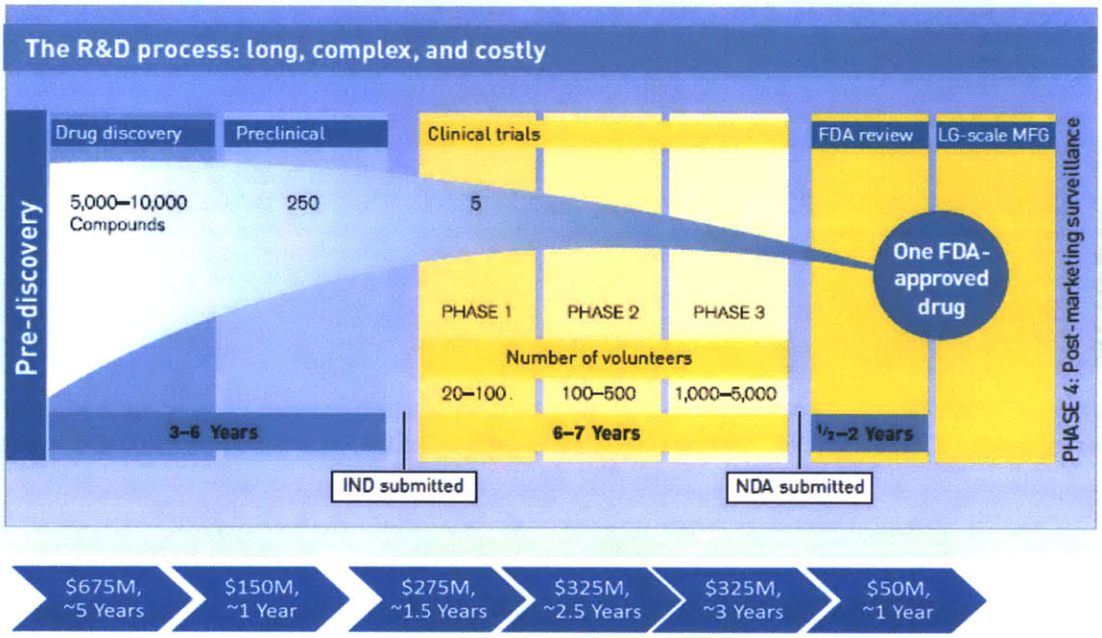


Fig. 2.4. Pharma R&D Process: Timelines, Attrition Rates, and Costs by Stage of R&D. (*Source: US FDA)*

The final regulatory step prior to market launch is filing for regulatory approval. In the United States, once a potential drug candidate has successfully completed all stages of the clinical trial process, the information gathered throughout the development process in the laboratory and its clinical trials is submitted to the FDA for review and approval. This process can take up to two years.

Scale-Up & Commercial Manufacturing

In addition to planning and conducting clinical trials, pharmaceutical companies must determine how to manufacture and distribute the new drug once approved. Of particular

interest in this context is the complexity and cost of the manufacturing process. The risks associated with manufacturing vary by drug class - drugs which are "small" molecules and are primarily organic compounds derived via synthetic chemistry, Vs. "large" molecules, which are primarily biological in origin, often in the form of naturally occurring proteins, enzymes, or antibodies.

For most pharmaceutical companies, the decision to invest in building a new manufacturing facility or scaling up existing manufacturing capacity is a critical one. Establishing new manufacturing capabilities is very capital intensive, and can take several years. Often, the capital required to build and obtain operational clearance from the FDA for a new manufacturing plant can exceed $1Billion, and take as many as three years. Given these factors, miscalculating the market potential of a yet-to-be-approved drug can be very costly.

Forecasting the demand, rate of acceptance, and eventual peak sales of any new medicine is a complex and imperfect science. The recent history of the pharmaceutical industry is replete with examples of erroneous forecasts that have led to significant negative outcomes for the involved companies. In late 1999 Immunex Corporation's breakthrough biological drug Enbrel was seen as a major biotech success, and became the treatment of choice for many forms of arthritis. Revenues from Enbrel surpassed $1 Billion in less than three years, and Immunex was named one of the fastest growing companies in the US. Multiple stock-splits were declared, and investors were euphoric about Immunex's prospects. Yet, the unprecedented demand for Enbrel caught Immunex by surprise, and the inability to meet market demand led to significant pressure on the company's stock price. By 2002, Immunex had been acquired by Amgen, another biotech success story. Amgen went on to build one of the most complex and expensive biotech manufacturing plants in the world to manufacture Enbrel in sufficient quantities. This new manufacturing plant was built at a cost of nearly $2 billion and was eventually approved by the FDA in the mid 2000's.

More recently, major problems in Genzyme's manufacturing plant for one of its flagship products led to significant disruption in the company's financial performance, and made it

vulnerable to an acquisition. In 2011, Sanofi, a major European pharmaceutical company acquired Genzyme to strengthen its' own biologics capabilities.

In addition to a complex, unpredictable, and demanding regulatory environment, intellectual property and market demand considerations are additional factors in determining access to prescription drugs, devices, and diagnostics on a global level.

Intellectual Property Considerations

As described earlier, the biopharmaceutical industry operates under a challenging business model. Companies must make significant investments in R&D, much of which will need to be made 10 to 15 years before the approval and market entry of any products. A significant element in assuring shareholders that these speculative investments are worthwhile is the promise of intellectual property protection. It is now reasonably well established that the drug pipelines of most companies are seen as speculative investments, with future cash flows at risk from a variety of factors, some predictable and others not so predictable. Until recently, intellectual property protection in the United States was considered highly predictable, and formed the backbone of the core R&D strategy of many biopharmaceutical companies.

The patent system in the United States is a major driver of innovation and commerce. Without it, bold entrepreneurs and established companies could not take the risk of making substantial early investments to develop and refine a successful product. More broadly, recent changes in the intellectual property landscape around the world have had a major impact on the biopharmaceutical industry.

We have stated before that R&D is not only expensive, but it is also risky. Only one in a thousand compounds that originate in discovery research reach clinical trials, and less than 20% of those compounds that are clinical trials gain approval form the FDA. Further, obtaining FDA approval is no guarantee of market success, and as shown earlier, only 20% of marketed drugs recoup their R&D costs. A logical question that follows is why would the industry embark on this process in the first place?

The larger societal implications of this fundamental question are the subject of much academic research. Suffice it to say that at some fundamental level, the biopharmaceutical industry is genuinely motivated by bringing life-changing, and in many instances life-saving drugs to patients who need them. Yet, in a market driven economic system, every company must also be held accountable to its shareholders. The protection, market exclusivity, and other incentives provided by a robust and efficient intellectual property system are key to enabling investors in making informed investment decisions that ultimately make it possible for companies to make the necessary investments.

An effective and robust intellectual property system must promote fair and meaningful incentives for innovation, it must provide a high degree of certainty to innovators regarding their rights under the system, and it must provide for a strong enforcement mechanism for resolving violations of intellectual property. The absence of any one of these essential elements can severely erode the confidence in the system, and drive innovation away.

In the next section, I examine the salient aspects of the intellectual property system as it impacts the biopharmaceutical industry. Recently, the industry has been the subject of much criticism for its relatively unyielding stance on intellectual property. At issue is the ability of non-innovator companies to make "copies" of the innovators drugs, and introduce these "generic" drugs into the market, thus driving prices down. Some would argue that the introduction of generics is a good thing since it reduces the overall cost of healthcare. In an environment where healthcare costs are a significant source of intellectual, political and even judicial debate, the role of an effective intellectual property system has become even more critical.

According to the World Intellectual Property Organization (WIPO), "Intellectual property refers to the exclusive rights granted by the State over creations of the human mind, in particular, inventions, literary and artistic works, distinctive signs and designs used in commerce. Intellectual property is divided into two main categories: **industrial property rights**, which includes patents, utility models, trademarks, industrial designs, trade secrets, new

varieties of plants and geographical indications; and **copyright and related rights**, which relate to literary and artistic works."

For the purposes of this study I will only focus on the "Industrial Property Rights", since this is most relevant to the biopharmaceutical industry. It is evident that Industrial property (IP) rights are extremely important for the pharmaceutical industry. The use of the IP system by the biopharmaceutical industry is driven by the inherent business strategy of the company - size, resources, innovative capacity, competitive context, global presence, global markets, and field of expertise.

Established innovator companies with major R&D investments aimed at developing new drugs or diagnostics rely heavily on the patent system to provide assurance that most of the R&D costs can be recouped. Emerging biotechnology companies and academic labs with novel ideas or molecules also rely on the patent system to secure fair licensing deals. A robust market in licensing is playing an increasingly important role in driving innovation in the biopharmaceutical industry. Finally, the protected public disclosure enabled by the patent system plays an important role in the further evolution of the innovation in the industry. Established and emerging companies rely on the availability of such information to determine whether they have the "freedom to operate" in shaping their own R&D strategy. Towards the end of the patent life of an innovator's drug, generics companies rely on the public knowledge to rapidly build the capabilities needed to introduce safe and efficacious generic copies of drugs, thus reducing the cost dramatically.

Patents

According to the WIPO, "A patent is an exclusive right granted by the State for an **invention** that is **new, involves an inventive step (or is non-obvious)** and is **capable of industrial application (or useful)**." (*Source: WIPO Guideline Document, 2011)* Once issued, the holder of a drug patent is given the exclusive right to make and sell the drug, and is able to prevent others from making, selling, or importing a foreign version of the same drug. Thus, an

issued patent is a very important business asset, and forms the basis of establishing a predictable cash flow from the newly marketed drug.

Most innovative drugs, medical devices, and diagnostics are typically filed under a "Utility Patent". In an effort to harmonize the intellectual property system world-wide, the United States Patent & Trademark Office (USPTO), and the WIPO have modified the rules governing Utility Patents. Under the new rules, all Utility Patents are generally issued for a period of *20 years from the date of filing*. This is an important change from the previous state, wherein patents were issued for duration of 17 years from initial disclosure. This change from "first to disclose" to "first to file" has had a dramatic impact on the intellectual property strategy of many companies in the biopharmaceutical industry. It is possible that an innovator company that is not vigilant about the state of scientific progress in its R&D efforts can be pre-empted by another company that files a patent application for a related product or molecule first.

In some countries, pharmaceutical products may be granted an additional period of patent protection to compensate for inefficiencies and delays in obtaining marketing approval from regulatory agencies. This is of particular significance in several emerging markets such as China, India, and Brazil, where regulatory approval and marketing approval for a new drug are granted by separate agencies.

Thus, without adequate intellectual property rights, competitors can easily copy hard won innovations in biopharmaceutical industry immediately, without incurring the major expense of R&D. This would negatively impact the innovator companies' ability to recoup their investments and would erode shareholder value, and make it difficult if not impossible, for the biopharmaceutical industry to justify making risky and expensive investments in developing new drugs.

The Impact of Patent Expiry

The existence of the intellectual property regime played an important role in enabling the biopharmaceutical industry to discover and market drugs that became extraordinary financial success stories. In the mid-1980s' SmithKline's proton pump inhibitor drug Tagamet, which was prescribed for the treatment of peptic ulcers became the first drug in the history of the industry to reach annual revenues of over $1 Billion. Glaxo's Zantac, another drug for the treatment of ulcers quickly went on to become a "blockbuster", achieving annual revenues of over $1B. The era of blockbuster drugs was born. Since then several drugs across many different therapeutic areas have gone on to become megs-blockbusters, with annual sales exceeding $3 billion or more. Pfizer's Lipitor which was a lead drug in a class of drugs called "Statins", went on to become the biggest commercial success of all, achieving annual sales of nearly $10 Billion.

The era of the blockbuster drugs led to a change in the overall cost structure of the biopharmaceutical industry. There was a dramatic increase in R&D expenditure, with well over $500 Billion being spent on developing new drugs by the top 15 global biopharmaceutical companies between 2000 and 2010. In many cases, this translated to an annual R&D expenditure of about 20% of revenue for most companies. Much of this money was being spent on every more risky areas of disease biology, with the allure of successfully launching more blockbusters into the market.

The complexity of the diseases being addressed by the newly approved drugs also meant that most companies had to invest heavily in building increasingly sophisticated sales & marketing organizations. The process of "detailing" a new drug to a prescribing physician required a well-trained and knowledgeable sales force, with specialized knowledge about the new drug. In addition, the biopharmaceutical industry embarked on an unprecedented campaign to bring awareness to patients by initiating a series of "direct to consumers (DTC)" campaigns. These DTC campaigns quickly transformed patients into consumers, and also brought in new patients who became better informed about medical conditions that they might

have previously been unaware of. DTC campaigns were very successful, and led to significant increases in the number of prescriptions written by physicians. It could be argued that some of the most successful drugs of the last decade, including Lipitor, Viagra (Pfizer), Enbrel (Amgen), Humira (Abbott) benefited dramatically form the enhanced sales and marketing efforts of these companies.

An unintended consequence of the tremendous market success of these drugs was the fact that the cost to the healthcare system from prescription drugs increased, with a seemingly direct correlation to the overall increase in healthcare costs. This is paradoxical, since in the case of drugs such as Lipitor, which helped to lower cardiovascular risk in a large number of patients, the reduced incidence of serious cardiovascular disease actually led to a reduction in related healthcare costs.

This cycle of increased spending – from R&D to Sales and Marketing, was largely driven by industry's desire to pursue the very profitable blockbuster drugs to solve unmet medical needs for diseases common to many millions of people, often at the expense of other drugs in the pipeline. This process of developing new drugs coincided with massive consolidation in the industry, with mega-mergers becoming the norm. The impetus for these mergers (ref) was the apparent productivity of the collective pipelines of the industry, and the seemingly enviable financial returns for the companies' shareholders.

However, the era of the blockbuster drug is ending. In the U.S. alone, branded pharmaceuticals accounting for some US$120 billion in annual revenues have recently come off patent (including Lipitor, Zyprexa, Plavix, and Seroquel) or will soon be coming off patent in the next few years. In almost every instance, generic equivalents of the innovator's drug have entered the market almost immediately, thus eroding a major source of the industry's profits.

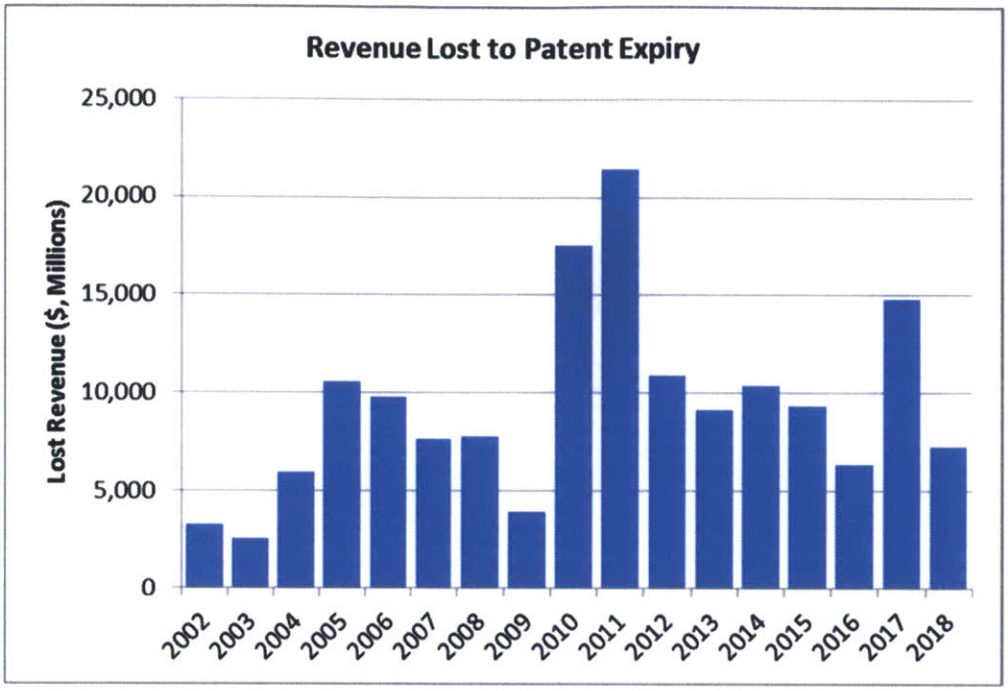


Fig. 2.5. Annual lost revenue due to patent expiry. (*Data Source: Evaluate Pharma)*

With the erosion in profits, the spending levels of the blockbuster era are unsustainable. While there is still much to be done to alleviate human suffering due to diseases for which no effective treatments are available, it is doubtful if the biopharmaceutical industry will be able to pursue this goal within the old model of developing exclusive medicines that can enjoy patent protection for many years.

Developing novel medicines for unsolved medical problems is increasingly difficult. More than ten years after decoding the human genome, much remains to be done in translating the breakthroughs in disease understanding brought upon by the Human Genome Project into useful treatments for many diseases.

We have described the increasing pressures felt by the biopharmaceutical industry from every direction — from regulators setting the rules for drug effectiveness and safety, from managed care organizations and employers pushing back on prescription drug costs and reimbursement, from competitors coming to market with alternative brands or generics, and from disgruntled shareholders. In addition, the number of promising molecules in the

collective pipelines of the industry is shrinking, and the risk/reward ratio for R&D spending is worsening. Overall, these trends have resulted in lower revenue, reduced profitability.

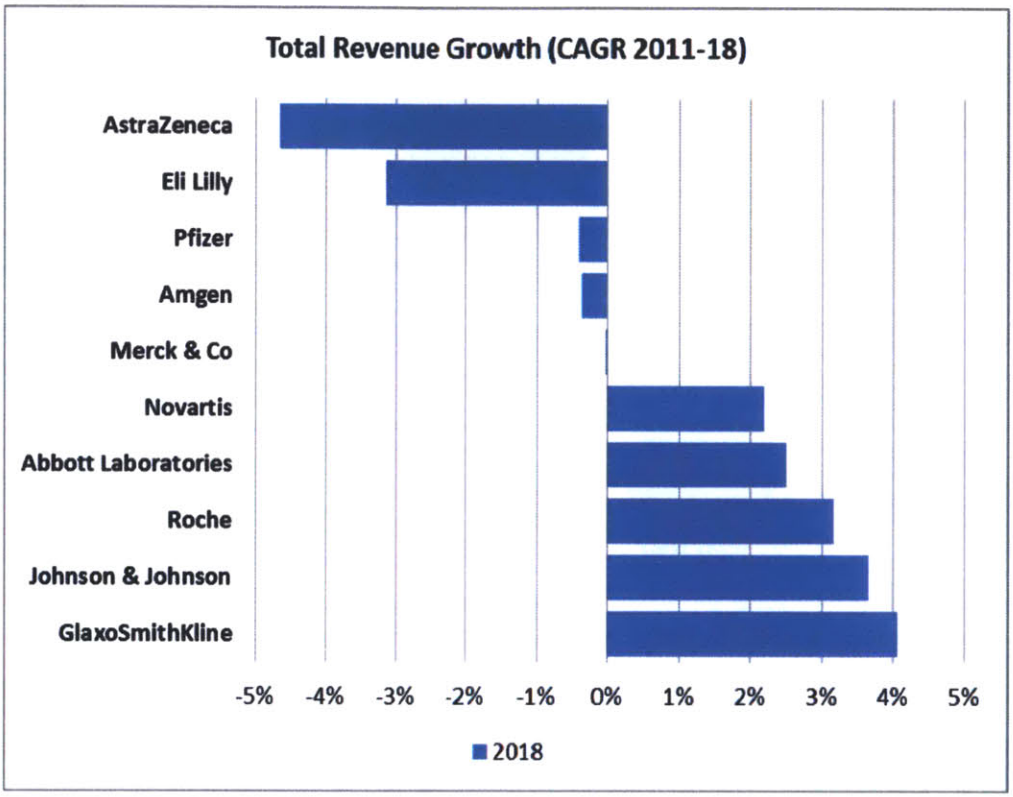


Fig. 2.6. Projected total revenue growth (CAGR 2011 – 2018) for the ten companies in the study. (*Data Source: Evaluate Pharma*)

Chapter 3

The primary objective of this brief, qualitative study was to provide an assessment of the incongruence between increased R&D spending by the biopharmaceutical industry, and the dramatic decline in productivity of the industry's pipeline in the corresponding time period. This study has focused on the decade beginning in 2000 and ending in 2010.

Ten global biopharmaceutical companies participated in this study. Table 3.1. lists the names of the companies and a summary of the key financial data of the ten companies. This data was obtained from publically available financial statements.

Table 3.1. Summary financial data for the companies included in this study. All financial data is in US$, Millions. (*Data Source: Company financial statements).*

Company	FCF (Pre-Div)	FCF Yield	Market Cap	Cash	Debt	Enterprise Value
Abbott Laboratories	9,140	8.5%	97,613	8,893	-18,219	106,939
Amgen	5,659	9.9%	55,046	19,374	-21,409	57,081
AstraZeneca	8,184	15.0%	55,092	10,000	-9,383	54,475
Eli Lilly	4,379	9.1%	47,879	4,925	-5,414	48,368
GlaxoSmithKline	9,334	7.3%	113,578	9,360	-23,282	127,500
Johnson & Johnson	14,557	8.9%	176,702	32,261	-19,627	164,068
Merck & Co	14,250	12.1%	115,671	14,972	-17,515	118,214
Novartis	13,982	9.9%	121,527	5,388	-24,594	140,733
Pfizer	18,448	10.1%	169,606	26,758	-38,949	181,797
Roche	11,980	7.2%	150,036	13,425	-29,405	166,016

Initial contact with each company was established through the office of Corporate Communications. The nature and purpose of the study was explained in a 30 minute telephone conference with an executive from the office of Corporate Communications. Eight of the ten companies agreed to provide a summary presentation on their R&D strategy, R&D budgets, and pipeline status. Two of the ten companies were unable to provide the requested information due to internal guidelines. In all cases, the information provided was available to the public, and no confidential information of material impact to the company's publically traded stock on any exchange in the United States or Europe was neither sought nor provided.

Each of the ten companies directed us to their public websites, wherein the R&D status, annual reports, financial statements, and other public disclosure documents available to shareholders were available. In addition to these data sources, I obtained in-depth research reports on each of these ten companies from selected major investment banks in the United States and Europe. Additional information for this study was obtained from the US-FDA and the European Medicines Agency (EMEA). Finally, a detailed review of the current peer-reviewed literature relevant to this study was conducted. All of this information is cataloged in Appendix A.

Abbott Laboratories

Abbott Laboratories is a diversified health care company with a more than 120 year history. Abbott's products include nutritional products, laboratory diagnostics, medical devices, and pharmaceutical therapies. Over the past decade Abbott has implemented a strategy to further diversify its range of products, global presence in R&D, and global markets for its products. Abbott has sales, manufacturing, research and development, and distribution facilities in several regions around the globe, with a focus on serving customers in the regions in which they live. Abbott is headquartered in Abbott Park, a suburb of Chicago, in the United States.

Table 3.2. Breakdown of revenue by business segment for Abbott Laboratories. (*Data Source: Evaluate Pharma)*

Abbott Laboratories (all financial data in US$ Millions)	2011	2018	CAGR
Rx Sales from Products module	18,935	14,492	-4%
Other Rx Sales	3,500	10,001	+16%
Total WW Prescription (Rx) Sales	**22,435**	**24,493**	**+1%**
Total WW Pharmaceuticals	**22,435**	**24,493**	**+1%**
Consumer Healthcare	6,006	8,709	+5%
Medical Devices & Healthcare Supply	9,934	12,287	+3%
Other Sales	476	689	+5%
Total WW Revenues	**38,851**	**46,179**	**+2%**

Abbott's therapeutic areas of focus in drug development include chronic kidney disease (CKD), neurosciences (degenerative diseases, pain), immunology (anti-viral therapies), oncology, diabetes, and inflammation. In a move to improve the performance of the company, and to better respond to the challenges faced by the industry, Abbott has announced that it will split into two independent companies, a research-based pharmaceutical company, and a diversified medical products company. This is a significant move, seen by many in the industry as key to Abbott's future financial success. The diversified medical products company will retain the Abbott name and will focus on nutritional products, diagnostics, and medical devices, while the research-based pharmaceutical company will focus on improving efficiencies and profit margins in developing and marketing novel drugs.

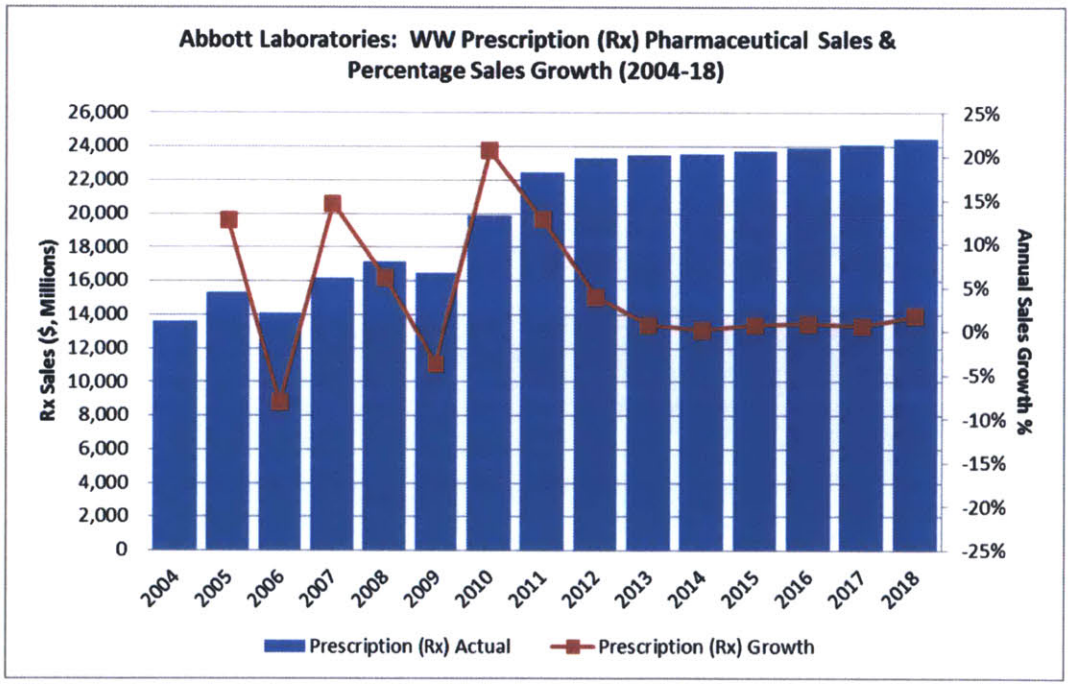


Fig. 3.1. Abbott Laboratories world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Abbott Labs, Evaluate Pharma)*

It is worth noting that Abbott expects its diversified medical products business to grow at a significantly higher rate, and has stated that the newly created research-based pharmaceutical company will have a diversified portfolio of small molecule and biological drugs,

and will have a greater focus on specialty products with smaller markets. In addition, this new company will expand its geographic presence by entering emerging markets with very different market dynamics and reimbursement policies.

Amgen Inc.

Amgen is a biotechnology pioneer and has the distinction of discovering and marketing the first biologic drug to achieve blockbuster status. Erythropoietin (EPO) is a biological drug that improves the ability of the human body to make more hemoglobin. This is critical for patients suffering from anemia, which may be caused by a number of diseases including kidney failure and cancer. Amgen was founded in the mid-1980s and is headquartered in Thousand Oaks, California.

Amgen's primary areas of disease focus include hematology, oncology, bone health, inflammation, and neurosciences. Amgen has diversified its portfolio of products to include small molecule therapeutics, and is striving to become an integrated pharmaceutical company.

Table 3.3. Breakdown of revenue for Amgen, Inc. (*Data Source: Evaluate Pharma)*

Amgen Inc. (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	15,237	14,559	-1%
Other Rx Sales	58	241	+23%
Total WW Prescription (Rx) Sales	**15,295**	**14,800**	**-0%**
Alliance/ Co-promotion Revenue	-	67	-
Royalty & Licensing Income	287	333	+2%
Total WW Pharmaceuticals	**15,582**	**15,200**	**-0%**
Total WW Revenues	**15,582**	**15,200**	**-0%**

Since Amgen went public, a hallmark of the company's performance was the exponential growth in annual revenue, primarily as a result of exploding sales of its blockbuster Erythropoietin and Neulasta franchises.

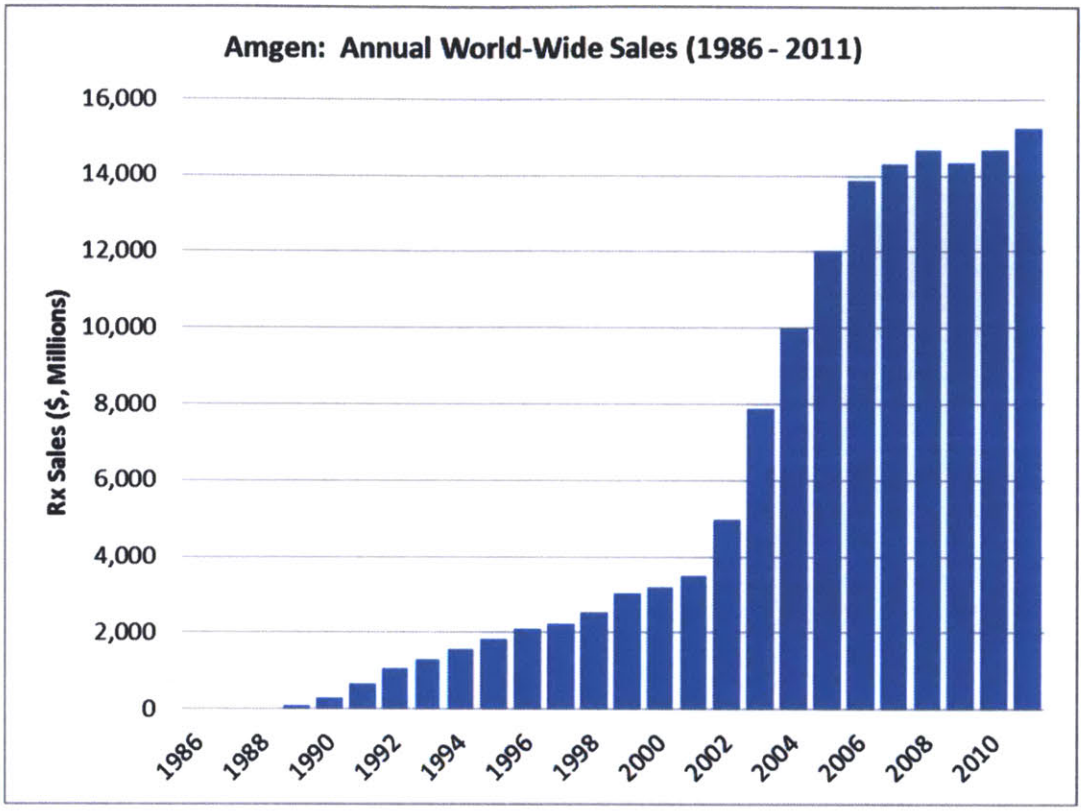


Fig. 3.2. Amgen Inc. world-wide prescription pharmaceuticals sales (1986 – 2011). *(Data Source: Amgen, Inc., Evaluate Pharma)*

However, since 2005 Amgen's share price has stagnated. This was driven in large measure by the systemic challenges faced by the industry, and the specific safety problems faced by Amgen's EPO franchise. Further, since 2007, Amgen has faced a number of regulatory setbacks related to the safety of its best-selling EPO franchise. The FDA review of the safety of EPO and Aranesp (a related product) led to revised "black-box" safety labeling on these products with a dramatic decline in the number of prescriptions written for these products. The resulting decline in revenue sent Amgen share price sharply lower, and resulted in significant shift in the overall R&D strategy of the company.

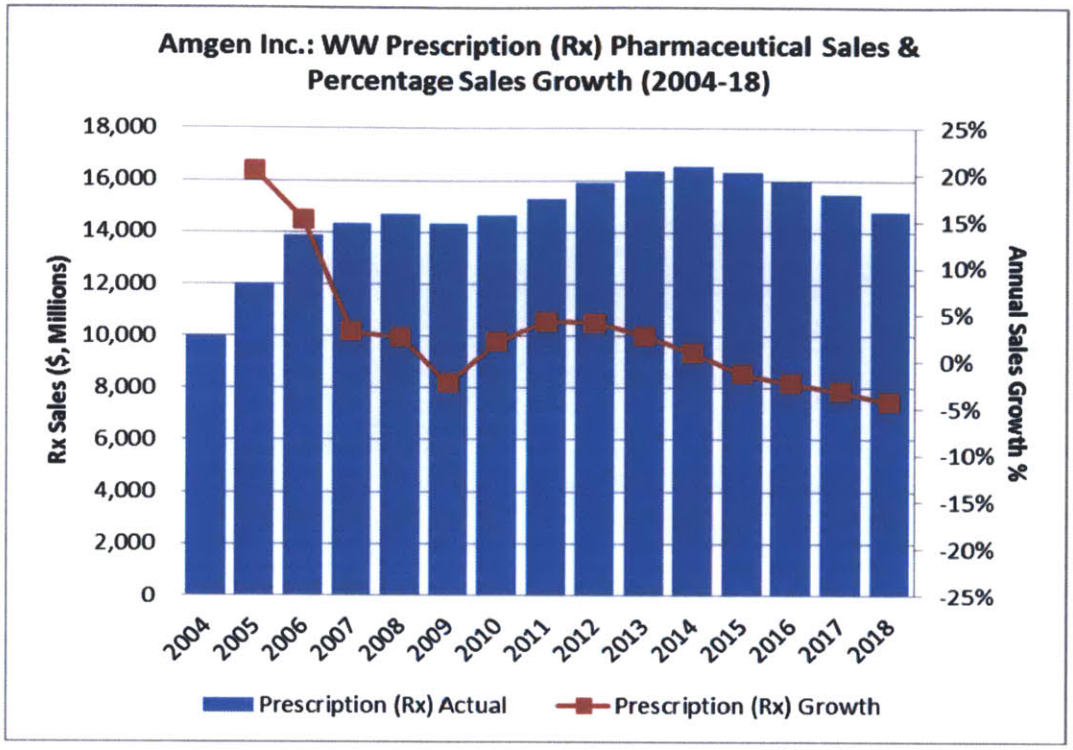


Fig. 3.3. Amgen Inc. world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Amgen, Inc., Evaluate Pharma)*

More recently, Amgen has successfully launched a breakthrough biological product to combat post-menopausal osteoporosis (PMO) in women, and to fight bone-metastasis in patients suffering from certain forms of breast and prostate cancer. However, it is unlikely that this biological product (branded as Prolia for the PMO indication, and Xgeva for the oncology indication) will ever reach the forecasted combined peak annual sales of over $3 billion. The development of this drug is an excellent example of the massive R&D investment and lengthy development process, with over $1.5 billion and 14 years invested in developing the drug.

Amgen's days as a darling growth stock of the biotech industry are over, and for the first time in its history Amgen declared a dividend in 2012 – yet another indication of slowing growth.

Astra Zeneca

AstraZeneca (AZ) is an Anglo-Swedish-American pharmaceutical company headquartered in London. United Kingdom. The present form of this company is a result of several mergers that occurred in the late 1990s and the early 2000s, when UK Based ICI Pharmaceuticals , merged with Swedish Pharma company Astra to form AstraZeneca.

Table 3.4. Breakdown of revenue for AstraZeneca by business segment. (*Data Source: AstraZeneca, Evaluate Pharma)*

AstraZeneca (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	31,382	20,615	-6%
Other Rx Sales	984	1,760	+9%
Total WW Prescription (Rx) Sales	**32,366**	**22,375**	**-5%**
Alliance/ Co-promotion Revenue	211	1,254	+29%
Royalty & Licensing Income	255	357	+5%
Other Pharmaceuticals	484	407	-2%
Total WW Pharmaceuticals	**33,316**	**24,393**	**-4%**
Healthcare Services	224	124	-8%
Medical Devices & Healthcare Supply	386	-	-
Eliminations/JV adjustment	-335	-437	+4%
Total WW Revenues	**33,591**	**24,080**	**-5%**

AstraZeneca invests nearly $4 billion in its R&D efforts every year. However, the return on this R&D investment has been significantly lower for AstraZeneca in comparison to most of its peers. Beginning in 2010, AstraZeneca has radically changed its R&D strategy and global R&D footprint. Several R&D sites including Södertälje (Sweden), Montreal (Canada), and Wilmington (USA) were shut down, with over 4000 R&D related job losses. Of particular significance is the fact that AstraZeneca has all but exited a core disease area – Neurosciences, in which it has had significant presence for many decades. A much smaller "virtual" neuroscience organization is now being formed, with most of the R&D being done by contract research organization.

AstraZeneca has a very aggressive partnering strategy, with a large number of global partnerships with academia and emerging biotech companies. AstraZeneca's strategic evolution has been driven largely by the fact that after a string of late stage failures in the clinic due to safety/efficacy, or economic issues, the company could no longer justify the massive expense of maintaining a relatively weak pipeline. Traditional markets in the West that could support major block-busters like Nexium simply did not exist any longer, and better financial performance meant that AstraZeneca needed to successfully enter emerging markets.

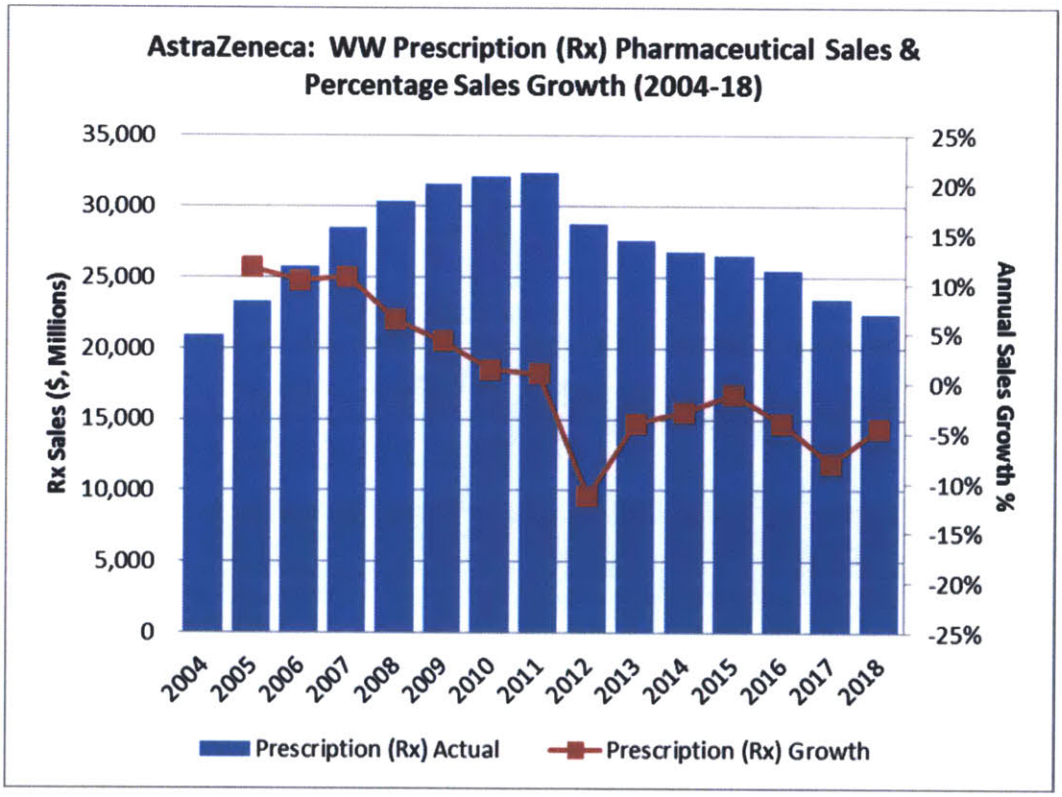


Fig. 3.4. AstraZeneca world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: AstraZeneca., Evaluate Pharma)*

AstraZeneca, like most of its peer group is now engaged cutting costs and becoming more efficient. Much of this reduction in cost is driven by major reductions in R&D expenditure. In a recent report in the Financial Times (April 2012), the productivity of the R&D efforts of several major European biopharmaceutical companies was reviewed. The study

compared the total R&D expenditure of each company between 2007 and 2011, and determined the NPV of new drug approvals in that same time period.

Between 2007 and 2011, AstraZeneca spent over $22.5 Billion in R&D and related areas. In the same time period, AstraZeneca had three new drug approvals, with an estimated NPV of $7.1 Billion. From a shareholders perspective, the cost per approved drug in this five-year period is much too high. This is emblematic of the core problem of declining R&D productivity in the face of increasing R&D expenditure. With the exception of Novartis, every company that was part of the study had similarly disappointing results.

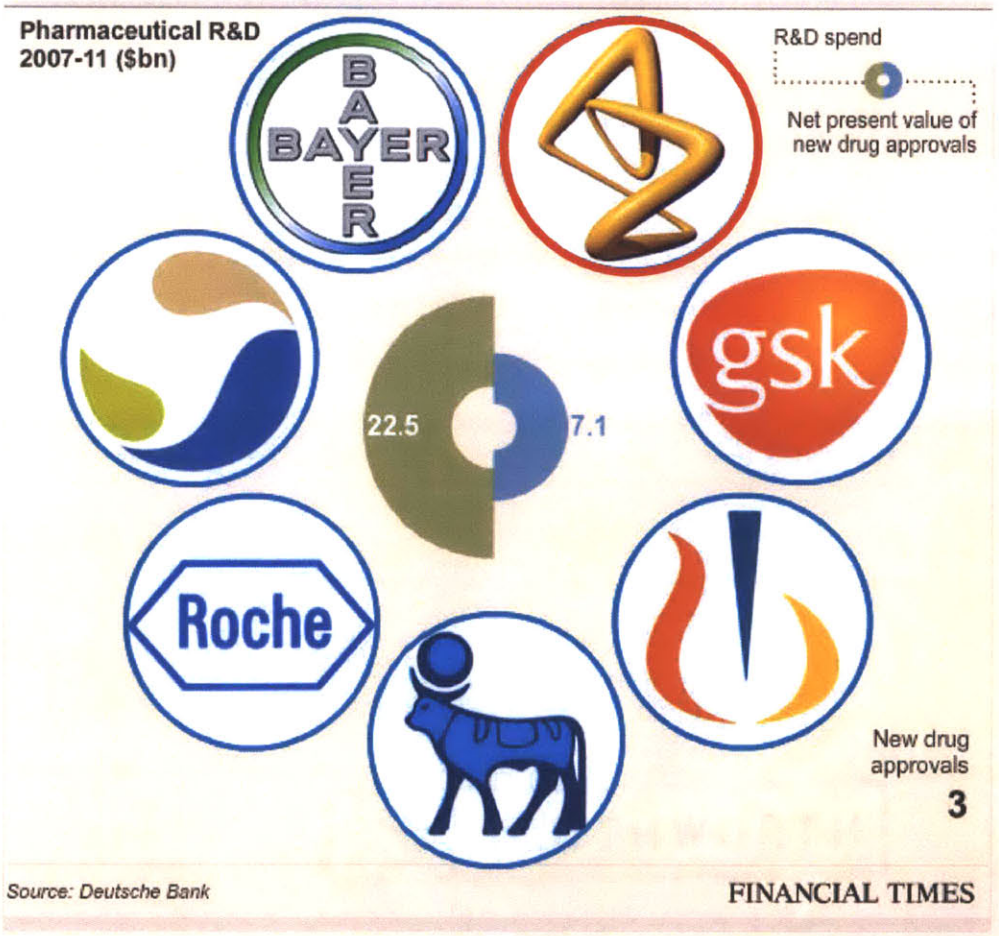


Fig. 3.5. Returns on R&D investment for AstraZeneca. A comparative study conducted by the Financial Times, April 2012. (*Source: Financial Times, April 2012).*

Eli Lilly & Company

Eli Lilly & Company (Lilly) is the 10th largest biopharmaceutical company in the world, and is headquartered in Indianapolis, USA. Lilly has remained independent over its 135-year history, and has focused on several therapeutic areas including diabetes, cardiovascular diseases, oncology, neurosciences, and urology.

Table 3.5. Breakdown of revenue for Eli Lilly & Co. by business segment. (*Data Source: Eli Lilly & Company, Evaluate Pharma).*

Eli Lilly & Company (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	20,363	13,408	-6%
Other Rx Sales	34	170	+26%
Total WW Prescription (Rx) Sales	**20,397**	**13,578**	**-6%**
OTC	1,249	1,512	+3%
Alliance/ Co-promotion Revenue	423	700	+7%
Royalty & Licensing Income	322	344	+1%
Other Pharmaceuticals	217	240	+1%
Total WW Pharmaceuticals	**22,608**	**16,373**	**-5%**
Consumer Healthcare	1,249	1,512	+3%
Agribusiness	1,679	3,064	+9%
Balancing OTC	-1,249	-1,512	+3%
Total WW Revenues	**24,287**	**19,438**	**-3%**

More recently, Lilly has added diseases of the emerging markets as a core area of R&D focus. In 2011, Lilly spent over $5 Billion in R&D, with a significant portion of that being directed to external partners. Lilly has been a leader in externalizing R&D, with substantial efforts in China and India. Lilly's "Chorus" R&D model was designed to encourage lower-cost partnerships in emerging markets that could provide a cost arbitrage, with the potential to enhance the value of its R&D efforts.

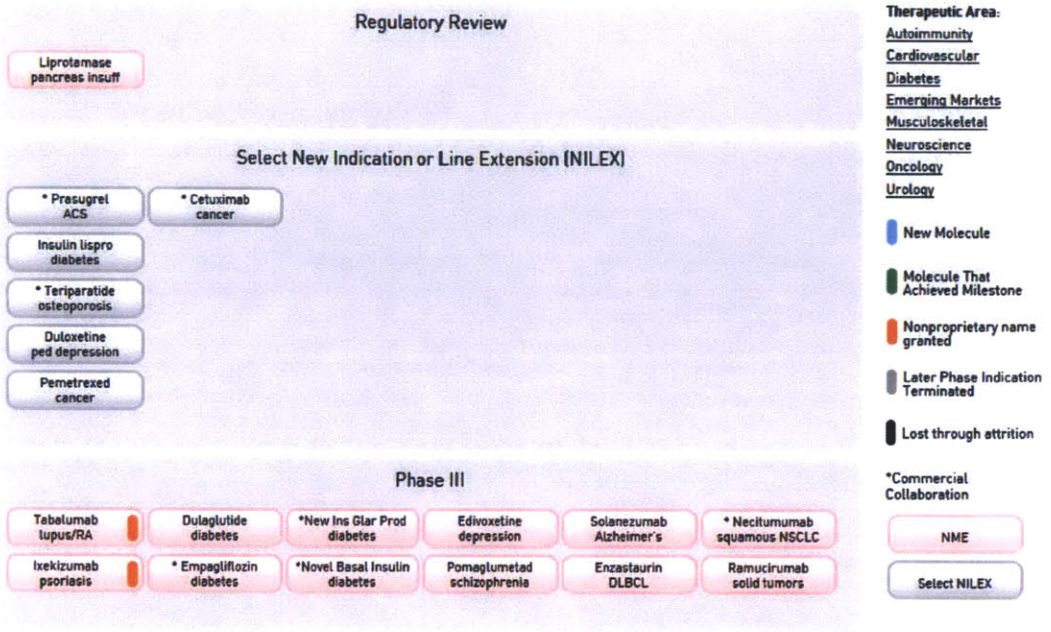


Fig. 3.6.. Lilly's pipeline, Q1'12. *(Source: Eli Lilly & Company)*

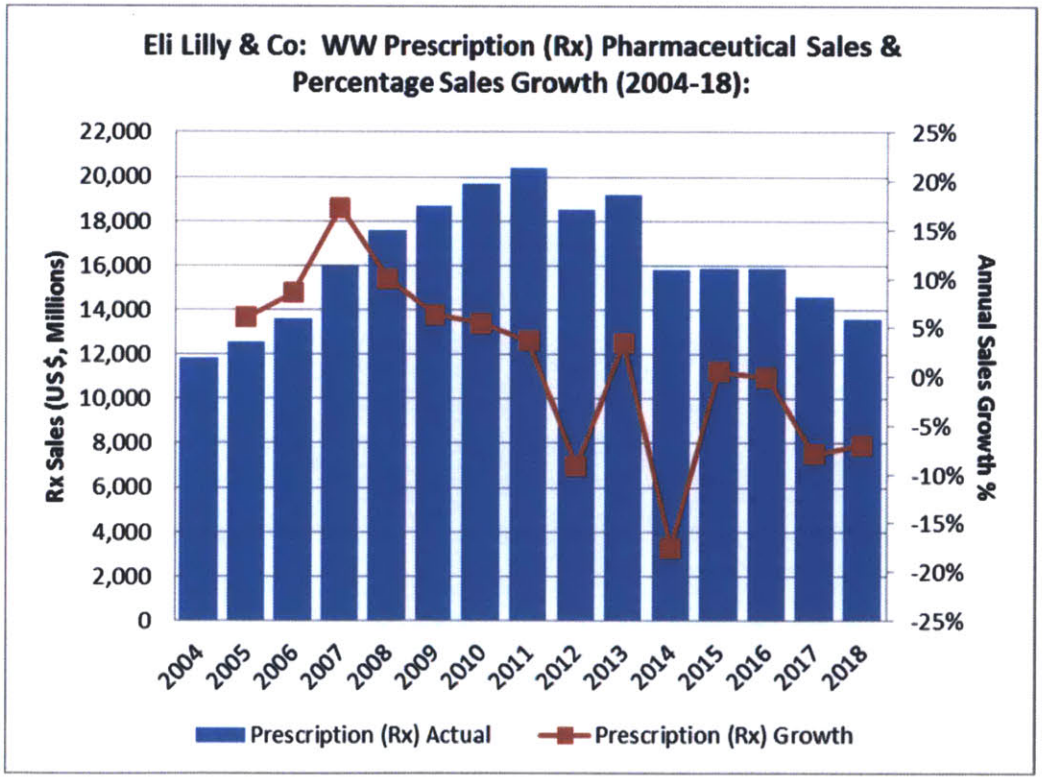


Fig. 3.7. Eli Lilly & Co.'s world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Eli Lilly & Co., Evaluate Pharma)*

GlaxoSmithKline

GlaxoSmithKline (GSK) is an Anglo-American biopharmaceutical company headquartered in London, UK. Since 2008, GSK has focused on growing a diversified global business with a presence in pharmaceuticals, consumer health, vaccines, and nutritional products. GSK was formed through a series of mega-mergers in the 1990s' and early 2000s'.

Table 3.6. Breakdown of revenue for GlaxoSmithKline by business segment. (*Data Source: GlaxoSmithKline, Evaluate Pharma).*

GlaxoSmithKline (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	19,257	25,476	+4%
Other Rx Sales	2,551	3,597	+5%
Total WW Prescription (Rx) Sales	**21,808**	**29,073**	**+4%**
OTC	2,453	2,993	+3%
Alliance/ Co-promotion Revenue	280	427	+6%
Royalty & Licensing Income	104	118	+2%
Total WW Pharmaceuticals	**24,645**	**32,610**	**+4%**
Consumer Healthcare	5,195	7,079	+5%
Balancing OTC	-2,453	-2,993	+3%
Total WW Revenues	**27,387**	**36,696**	**+4%**

In the years immediately following the formation of GSK, the company underwent a radical transformation in its R&D strategy. GSK was one of the earliest companies to recognize that the productivity of its R&D investments was on the decline. Through a series of strategic partnerships and alliances, GSK has built a diversified pipeline with an increased focus on developing new drugs that can be brought to the market at a significantly lower cost. Despite this, in the period between 2007 and 2011, GSK still had an overall negative NPV on its R&D investments.

Fig .3.8. Returns on R&D investment for GlaxoSmithKline. A comparative study conducted by the Financial Times, April 2012. *(Source: Financial Times, April 2012).*

GSK is one of the few global biopharmaceutical companies with a strong presence in the development and marketing of vaccines for various illnesses that impact the emerging markets. In 2011, GSK's R&D expenditures were approximately $4 Billion in pharmaceuticals, and $1 Billion in Vaccines. The global expansion of its pharmaceutical and vaccines franchises combined with a rapidly growing presence in consumer healthcare is likely to put GSK in a better position than many of its peer companies.

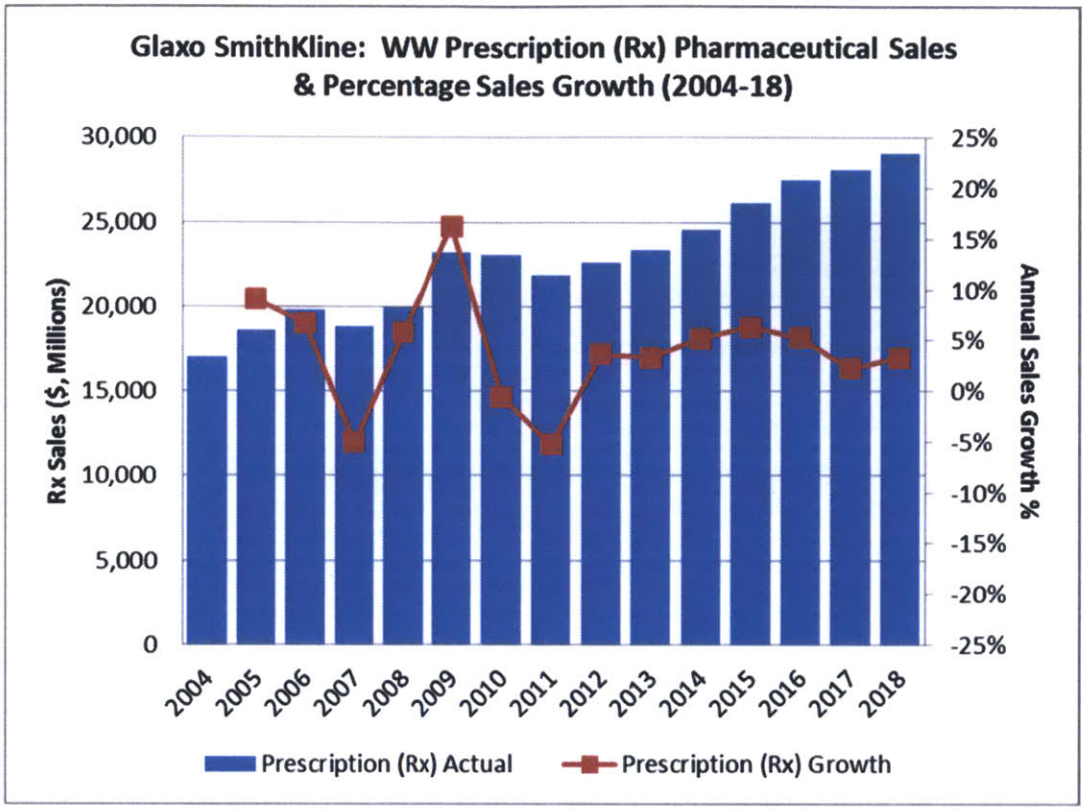


Fig. 3.9. Glaxo SmithKline's world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: GSK, Evaluate Pharma).*

Johnson & Johnson

Johnson & Johnson (JNJ) is a diversified healthcare company with a strong presence in multiple market segments related to human health. J&J is headquartered in New Brunswick (New Jersey), USA, and is the world's largest and most diverse medical devices and diagnostics company, the world's eighth-largest pharmaceuticals company, and the world's fifth-largest biologics company. Unlike most other companies in this sector, J&J is composed of over 250 operating companies in over 60 countries. In 2011, J&J's collection of pharmaceutical companies invested over $5.1 billion in R&D to develop new medicines to treat serious and widespread diseases, with a focus on multiple therapeutic areas including cardiovascular & metabolism, immunology, infectious diseases & vaccines, neuroscience & pain, and oncology.

Table 3.7. Breakdown of revenue for Johnson & Johnson by business segment. (*Data Source: Johnson & Johnson, Evaluate Pharma).*

Johnson & Johnson (all financial data is in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	20,149	24,871	+3%
Other Rx Sales	2,155	2,212	+0%
Total WW Prescription (Rx) Sales	**22,304**	**27,083**	**+3%**
OTC	2,585	3,158	+3%
Alliance/ Co-promotion Revenue	78	200	+14%
Royalty & Licensing Income	1,987	2,733	+5%
Total WW Pharmaceuticals	**26,953**	**33,173**	**+3%**
Consumer Healthcare	14,883	18,177	+3%
Medical Devices & Healthcare Supply	25,779	35,487	+5%
Balancing OTC	-2,585	-3,158	+3%
Total WW Revenues	**65,030**	**83,680**	**+4%**

Johnson & Johnson is perhaps the most diversified of all healthcare companies in the world. The combined strength of J&J's prescription medicines business, and its medical devices, diagnostics, and consumer healthcare businesses are likely to position J&J as one of the leaders in the next decade. J&J's global brand recognition, diversified distribution channel, and

supply chain expertise will be key strategic advantages as it expands its presence in emerging markets.

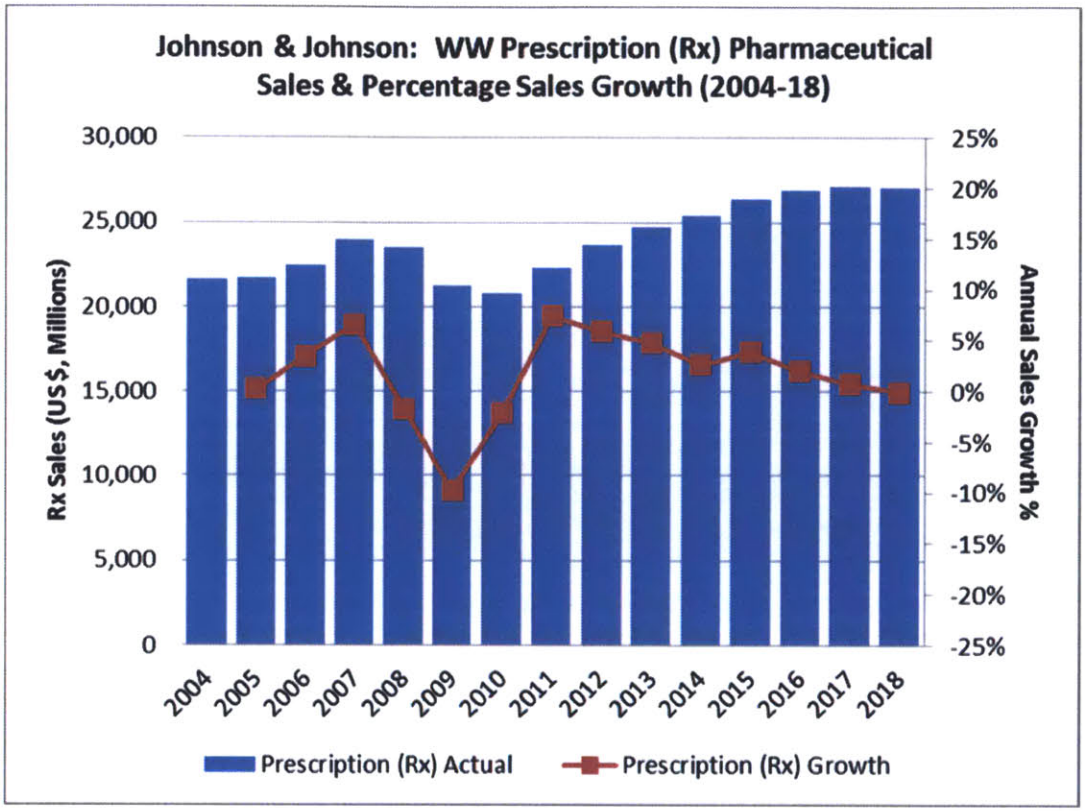


Fig. 3.10. Johnson & Johnson's world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Johnson & Johnson, Evaluate Pharma).*

Merck & Company

Merck & Co is an American pharmaceutical company and is headquartered in Whitehouse Station, (New Jersey), USA. Once considered one of the most innovative and progressive biopharmaceutical companies in the world, Merck went through what was perhaps the most painful period in its long history during the mid-2000s' in the wake of the catastrophic withdrawal of one of its best selling drugs, Vioxx. The story of Vioxx is as much about the issues faced by the entire biopharmaceutical industry, as it is about Merck. Celebrated as a true breakthrough in the treatment of pain, Vioxx offered hope to millions who suffered from chronic pain. However, when previously unseen adverse events emerged in the patient population at large, Vioxx was withdrawn voluntarily be Merck, leading to a prolonged period of under-performance and costly legal issues for Merck. By 2009, Merck's once stellar R&D organization was a shadow of its former self, with a pipeline that seemed to be amongst the worst in the industry

Table 3.8. Breakdown of revenue for Merck & Co. by business segment. (*Data Source: Merck & Company, Evaluate Pharma).*

Merck & Co. (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	40,244	38,921	-0.48%
Other Rx Sales	1,631	1,775	+1.21%
Total WW Prescription (Rx) Sales	**41,875**	**40,696**	**-0.41%**
OTC	511	566	+1.47%
Alliance/ Co-promotion Revenue	61	397	+30.62%
Royalty & Licensing Income	1,184	96	-30.17%
Other Pharmaceuticals	421	327	-3.52%
Total WW Pharmaceuticals	**44,052**	**42,083**	**-0.65%**
Consumer Healthcare	1,871	2,227	+2.52%
Agribusiness	3,253	4,926	+6.11%
Balancing OTC	-511	-566	+1.47%
Eliminations/JV adjustment	-618	-633	+0.34%
Total WW Revenues	**48,047**	**48,036**	**-0.00%**

In 2009, Merck did what many other companies before it had done when faced with an unproductive pipeline – they acquired Schering Plough, another ailing pharmaceutical company that offered some potential synergies in the operations, and a small pipeline of drugs which could bolster Merck's own pipeline. The combined company has embarked on a new strategy, focusing on a smaller number of disease areas, enhancing its leading position in vaccines development, and expanding its scope and operations into several emerging markets. Merck invests over $4 billion in R&D annually, and has been working to improve its overall cost structure. A number of R&D sites around the world have been closed, and more external partnerships are planned.

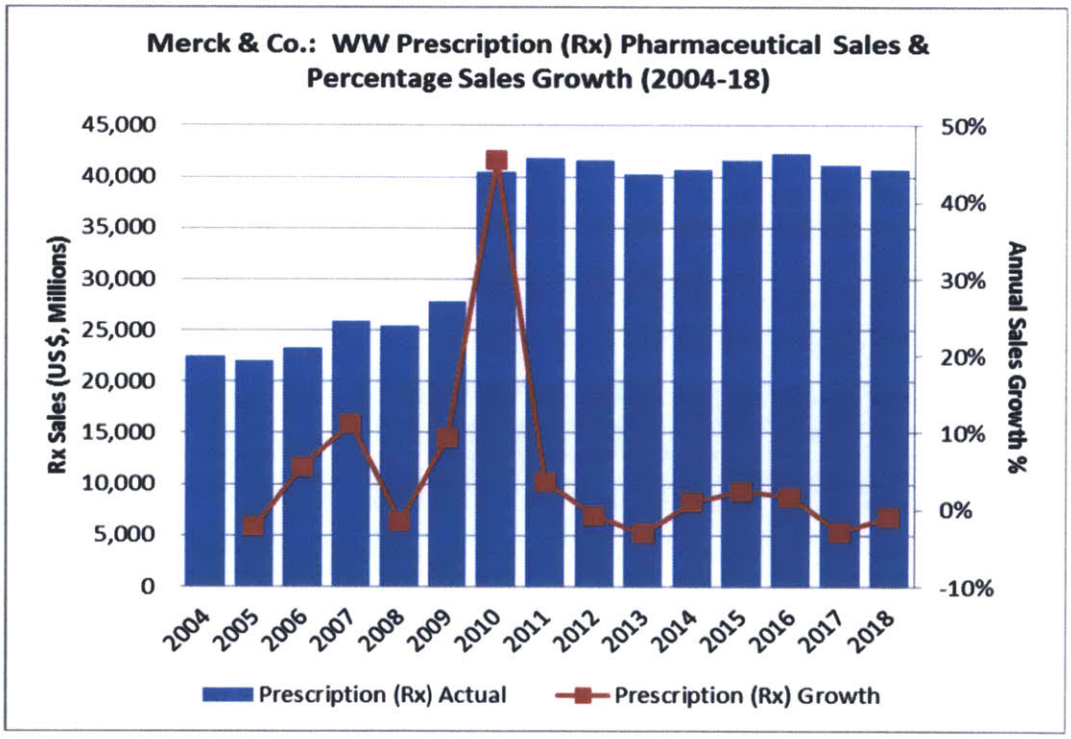


Fig. 3.11. Merck & Co.'s world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Merck & Co., Evaluate Pharma).*

It is evident form Fig. 3.11. that Merck's revenue growth for the foreseeable future will be weak. The 45% revenue spike in 2010 was the result of Merck's acquisition of Schering Plough, and is unlikely to be repeated in the future.

Novartis Pharmaceuticals

Novartis is a global biopharmaceutical company headquartered in Basel, Switzerland, and was formed in 1996 as a result of a mega-merger between Ciba Giegy & Sandoz Pharmaceuticals. Novartis has a strong culture of being an innovation driven pharmaceutical company, and is foremost amongst its peers in aggressively managing the multiple challenges faced by the industry. It is perhaps the best managed global biopharmaceutical company, and is widely regarded as a formidable competitor.

Table 3.9. Breakdown of revenue for Novartis by business segment. (*Data Source: Novartis, Evaluate Pharma).*

Novartis (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	35,316	33,194	-1%
Other Rx Sales	11,359	17,675	+7%
Total WW Prescription (Rx) Sales	**46,675**	**50,869**	**+1%**
of which WW Unbranded Generics	8,574	11,719	+5%
OTC	3,327	4,420	+4%
Alliance/ Co-promotion Revenue	15	-	-
Other Pharmaceuticals	1,708	2,169	+3%
Total WW Pharmaceuticals	**51,726**	**57,458**	**+2%**
Consumer Healthcare	3,327	4,420	+4%
Medical Devices & Healthcare Supply	6,448	10,241	+7%
Agribusiness	1,304	1,725	+4%
Balancing OTC	-3,327	-4,420	+4%
Eliminations/JV adjustment	-103	-133	+4%
Total WW Revenues	**59,375**	**69,290**	**+2%**

Novartis has a well-established strategy of becoming the leading innovator company in each of its core disease areas which include oncology, metabolic diseases, immunology, neurosciences, and vaccines. In addition, Novartis has established a leadership position in several emerging markets including China and India. Further, through its Sandoz subsidiary,

Novartis is also a dominant player in the global generics business, and has demonstrated that it can effectively manage revenue losses due to patent expiry.

Fig. 3.12. Returns on R&D investment for Novartis. A comparative study conducted by the Financial Times, April 2012. *(Source: Financial Times, April 2012).*

The recent Financial Times study concluded that between 2007 and 2011, Novartis had the most productive R&D strategy, with a significant positive NPV ($37.7 billion) with 15 new drug approvals, and R&D expenditures of $28.7 billion. As stated earlier, Novartis's strategic decision to grow its generics business will be a key factor in sustaining revenue in the future. In my view, of the ten companies that I studied, Novartis is best positioned to reduce the impact of patent expiry of its major drugs. In addition, Novartis's portfolio if current future drugs appears to be more diversified by therapeutic class and peak revenue.

Table 3.10. Novartis's top ten products by estimated revenue in 2018. *(Data Source: Novartis).*

Rank	Product	Therapeutic Subcategory	2011	2018	CAGR	Total Change	Phase (Current)	Patent Expiry
1	Tasigna	Other cytostatics	716	2,525	+20%	+1,809	Marketed	Jul 2023
2	Lucentis	Eye preparations	2,050	2,430	+2%	+380	Marketed	-
3	Afinitor	Other cytostatics	443	2,303	+27%	+1,860	Marketed	Sep 2019
4	Gilenya	MS Therapies	494	1,946	+22%	+1,452	Marketed	Feb 2019
5	Diovan	Angiotensin II antagonists	5,665	1,621	-16%	-4,044	Marketed	Sep 2012
6	Galvus	Anti-diabetics	677	1,398	+11%	+721	Marketed	Dec 2019
7	Bexsero	Vaccines	-	1,060	n/a	+1,060	Filed	-
8	Gleevec	Other cytostatics	4,659	1,054	-19%	-3,605	Marketed	Jul 2015
9	Exforge	Angiotensin II antagonists	1,209	950	-3%	-259	Marketed	Sep 2012
10	Sandostatin LAR	Pituitary & Hypothalamic hormones	1,443	911	-6%	-532	Marketed	Mar 2005
Other			18,843	18,007	-1%	-836		
Total			36,199	34,205	-1%	-1,994		

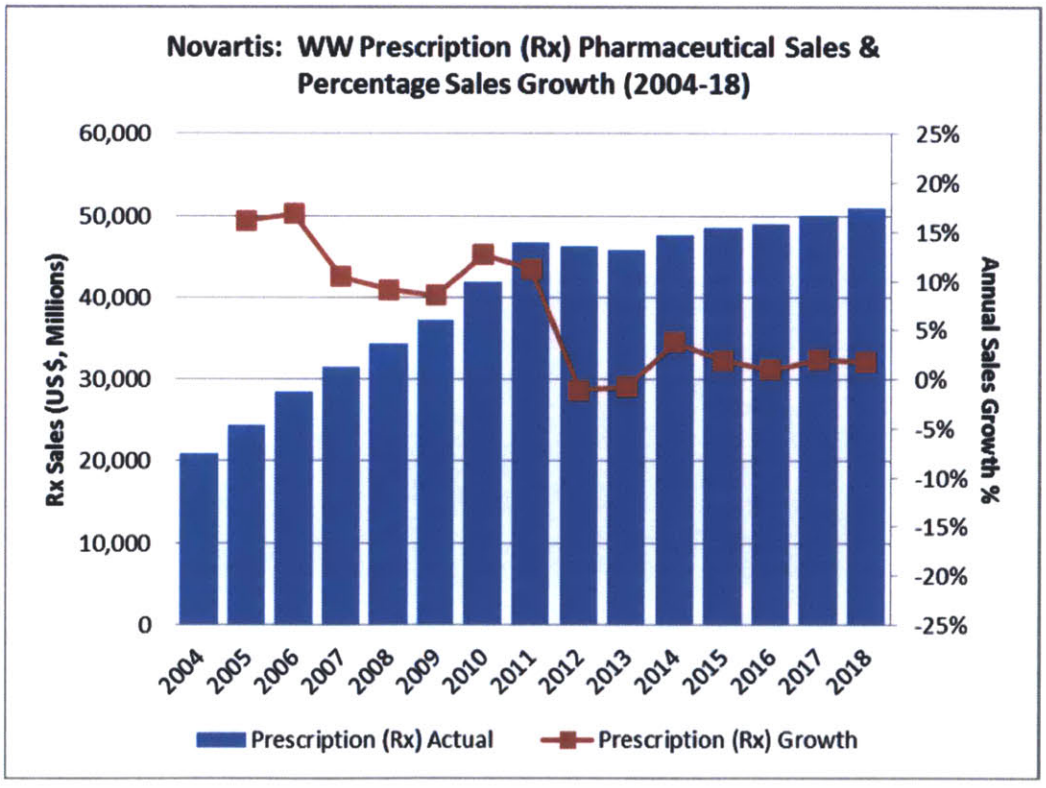


Fig. 3.13. Novartis's world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Novartis, Evaluate Pharma).*

Pfizer Inc.

Pfizer is the world's largest biopharmaceutical company and is headquartered in New York City, USA. Founded in 1849, Pfizer is a global leader in health with products that span the entire range of human health. Pfizer has created two distinct research organizations – The PharmaTherapeutics Research & Development group with a focus on discovering and developing small molecule therapeutics, and The BioTherapeutics Research & Development Group with a focus on large-molecule research, including vaccines.

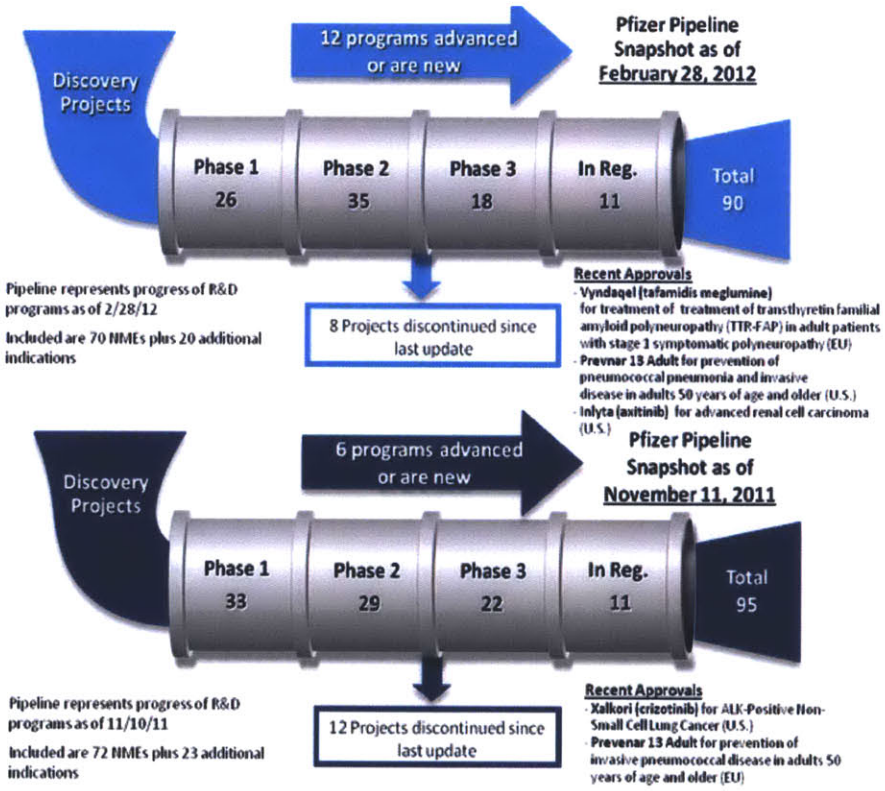


Fig. 3.14. A snapshot of Pfizer's drug development pipeline, Feb 2012. *(Source: Pfizer)*

Pfizer has had a history of engaging in major M&A activity and has acquired several companies over the past 15 years, including Warner-Lambert, Pharmacia-Upjohn, and most recently, Wyeth Pharmaceuticals. This strategy was very successful in boosting Pfizer to the top of the industry. Lipitor, the most successful pharmaceutical product ever, was brought into

Pfizer's pipeline from its acquisition of Warner-Lambert. Until November 2011, when Lipitor came off patent, it had reached annual global sales of nearly $10 billion.

Table 3.11. Breakdown of revenue for Pfizer by business segment. (*Data Source: Pfizer, Evaluate Pharma).*

Pfizer (all financial data in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	49,276	41,112	-2.6%
Other Rx Sales	4,271	5,787	+4.4%
Total WW Prescription (Rx) Sales	**53,547**	**46,899**	**-1.9%**
OTC	1,307	1,598	+2.9%
Alliance/ Co-promotion Revenue	3,630	3,874	+0.9%
Royalty & Licensing Income	570	524	-1.2%
Other Pharmaceuticals	299	296	-0.2%
Total WW Pharmaceuticals	**59,353**	**53,190**	**-1.6%**
Consumer Healthcare	5,195	7,417	+5.2%
Agribusiness	4,184	6,614	+6.8%
Balancing OTC	-1,307	-1,598	+2.9%
Total WW Revenues	**67,425**	**65,622**	**-0.4%**

Pfizer, and many other companies have tried to reproduce the commercial success of Lipitor, but have not succeeded. Importantly, the allure of developing and marketing a mega-blockbuster drug like Lipitor led Pfizer and most other major pharmaceutical companies to enter a period of unsustainable R&D expenditure. In its quest to develop and market multiple blockbusters, Pfizer has faced a string of expensive late-stage failures, with several products failing to meet FDA requirements in Phase II and Phase III, the most expensive stages of clinical development. Pfizer's recent acquisition of Wyeth was meant to bolster its pipeline, and provide a much needed revenue boost in the face of generic competition for Lipitor.

Table 3.12. Pfizer's top ten products by estimated revenue in 2018. (*Data Source: Pfizer).*

Rank	Product	Therapeutic Subcategory	2011	2018	CAGR	Total Change	Phase (Current)	Patent Expiry
1	Prevnar 13	Vaccines	3,657	6,715	+9%	+3,058	Marketed	-
2	Lyrica	Anti-epileptics	3,693	3,726	+0%	+33	Marketed	Dec 2018
3	Enbrel	Other anti-rheumatics	3,666	3,211	-2%	-455	Marketed	Oct 2012
4	Tofacitinib	Other anti-rheumatics	-	2,138	n/a	+2,138	Filed	-
5	Sutent	Anti-angiogenics	1,187	1,475	+3%	+288	Marketed	Feb 2021
6	Lipitor	Anti-hyperlipidaemics	9,577	1,387	-24%	-8,190	Marketed	Nov 2011
7	Viagra	Sexual dysfunction	1,981	1,303	-6%	-678	Marketed	Oct 2019
8	Xalkori	Other cytostatics	19	1,150	+80%	+1,131	Marketed	Oct 2029
9	Pristiq	Anti-depressants	577	1,011	+8%	+434	Marketed	Feb 2022
10	Norvasc	Calcium antagonists	1,445	1,000	-5%	-445	Marketed	Mar 2007
Other			24,782	19,594	-3%	-5,187		
Total			50,584	42,710	-2%	-7,874		

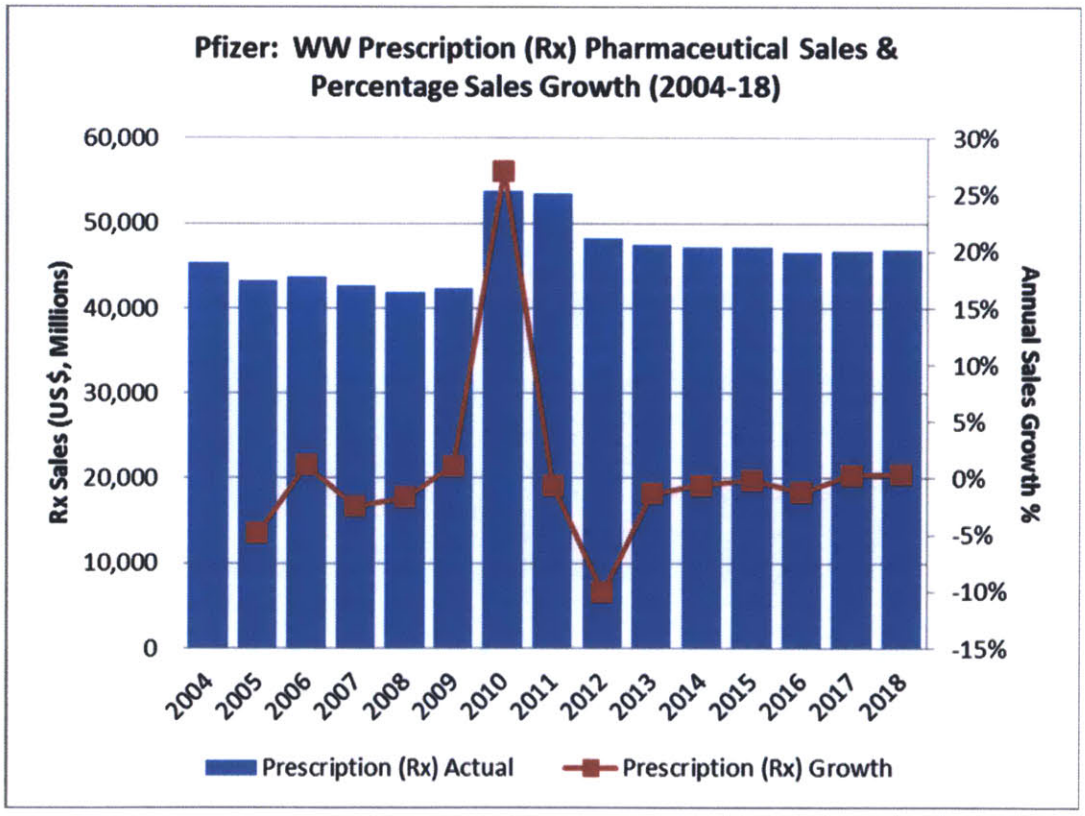


Fig. 3.15. Pfizer's world-wide prescription pharmaceuticals sales and projected growth (2004 – 2018). *(Data Source: Pfizer, Evaluate Pharma).*

As shownin Fig. 3.15., Pfizer's acquisition of Wyeth in 2009 gave it a big boost in revenue from that was seen in 2010. However, the loss of patent life (November 2011) for Lipitor, the biggest-selling drug of all time with annual sales in excess of $10 billion is expected to lead to a steep drop in revenue in 2012 and beyond. When we project revunes in 2018, it is clear that the reliance on revenue growth from a a small number of blockbusters can have a huge negative impact in the long run.

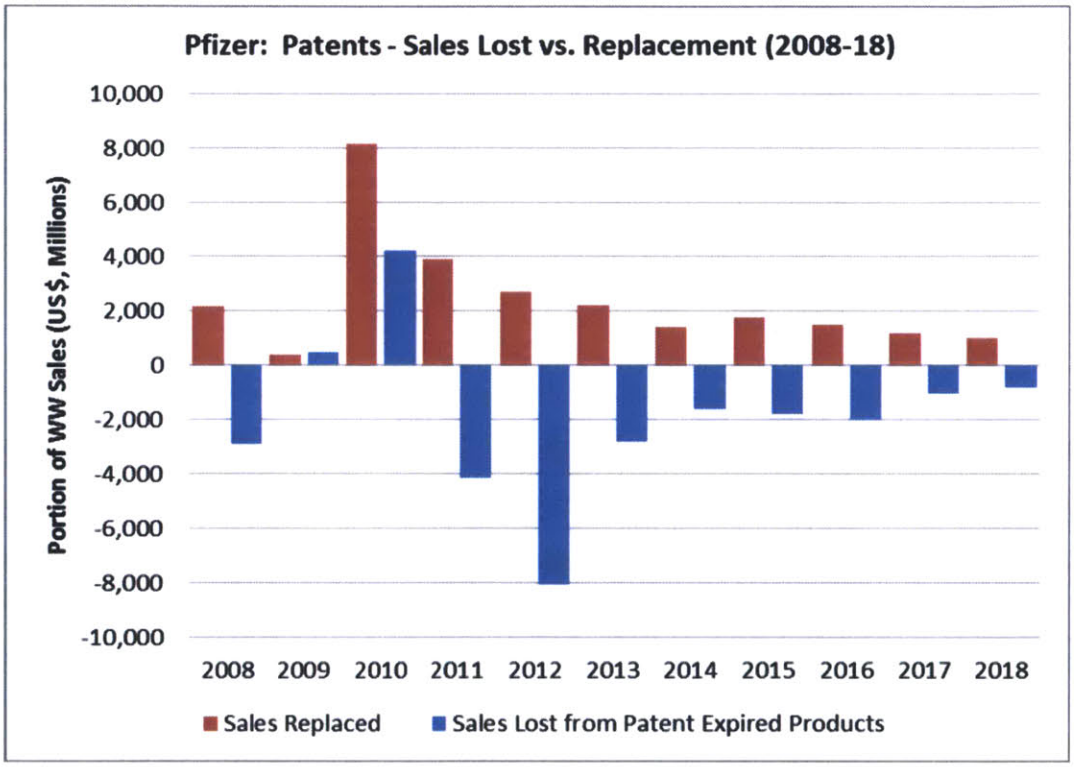


Fig. 3.16. Pfizer's Patents: Sales lost Vs. replacement, 2008 - 2018 *(Data Source: Pfizer, Evaluate Pharma).*

It is worth emphasizing again that the future does indeed look very challenging for the world's largest pharmaceutical company. Pfizer's predicament might trigger another round of major M&A activity. However if such M&A activity is driven by the business model of the past decade, it is unlikely to succeed.

Roche Holdings

Roche Holdings is a diversified global healthcare company headquartered in Basel, Switzerland. Roche is the world's leading oncology company, and the world's number one *in vitro* diagnostics company. With its combined strength in diagnostics and pharmaceuticals, Roche aims to become the most effective company in personalized medicine. In the face of the numerous challenges that the industry faces, Roche believes that its strategy of developing drugs which are proven to be more efficacious and safe by the use of appropriate diagnostics will lead to a reduction in the overall development costs of new drugs.

Table 3.13. Breakdown of revenue for Roche by business segment. (*Data Source: Roche, Evaluate Pharma).*

Roche (all financial data is in US $, Millions)	2011	2018	CAGR
Rx Sales from Products module	29,848	37,526	+3%
Other Rx Sales	2,907	3,354	+2%
Total WW Prescription (Rx) Sales	**32,755**	**40,880**	**+3%**
Alliance/ Co-promotion Revenue	-	21	-
Royalty & Licensing Income	39	45	+2%
Total WW Pharmaceuticals	**32,794**	**40,946**	**+3%**
Medical Devices & Healthcare Supply	9,737	13,664	+5%
Total WW Revenues	**42,531**	**54,609**	**+4%**

In 2011, Roche invested nearly $8 billion in R&D, making it the leading R&D investor in the biopharmaceuticals sector. In 2009, Roche completed its acquisition of the outstanding shares of Genentech, a global biotechnology pioneer. This move marked the end of a turbulent period for Roche – a period in which the productivity of its R&D pipeline significantly below par. It is important to note that the figures presented in Table 3.13 are for Roche's core Pharma business and do not include the revenues from Roche's diagnostics business.

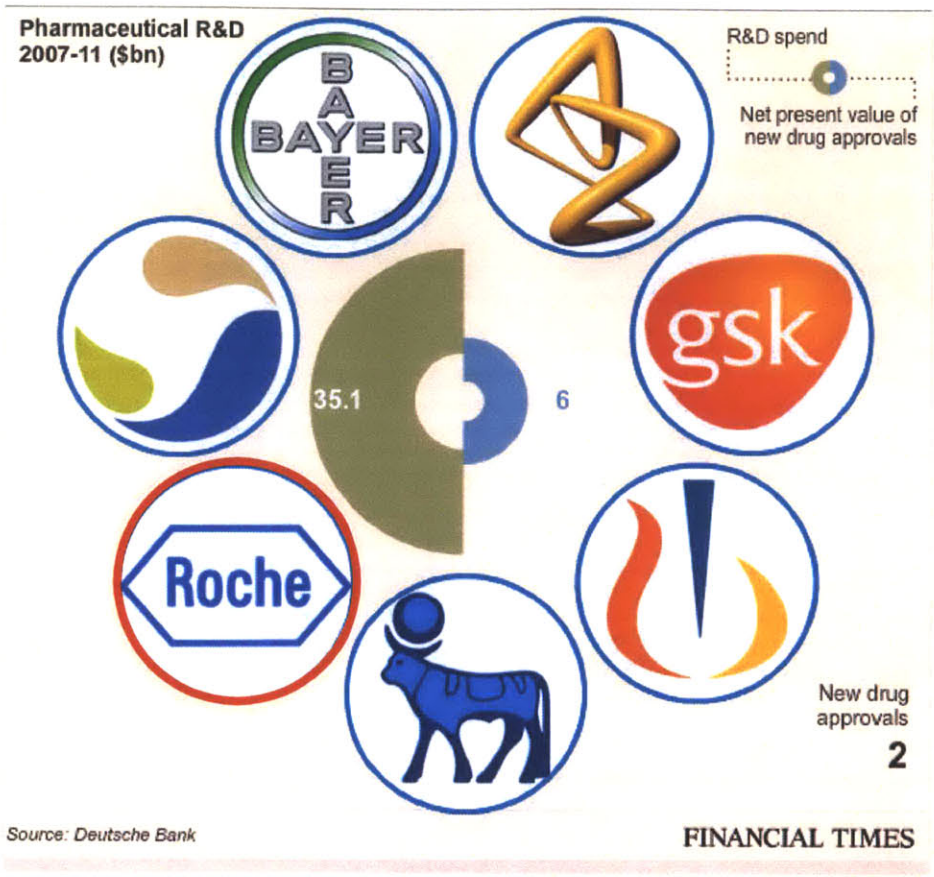


Fig. 3.17. Returns on R&D investment for Roche. A comparative study conducted by the Financial Times, April 2012. (*Source: Financial Times, April 2012)*

As shown above, Roche has had a particularly unproductive period between 2007 and 2011, with only two new drug approvals, and a substantially negative return on its R&D investments. Recent restructuring and cost cutting efforts may indicate that Roche is becoming more effective at leveraging its R&D investments.

Another significant factor in determining Roche's future success will depend on Roche's ability to diversify its revenue base. A significant portion of Roche's revenue – expected to be over 65% in 2018 – is derived from its oncology and immunology products. While effective, most of these products are priced beyond the reach of patients in emerging markets. Roche's focus on oncology therapeutics is important in the battle against cancer, but it is unclear if this strategy is sustainable.

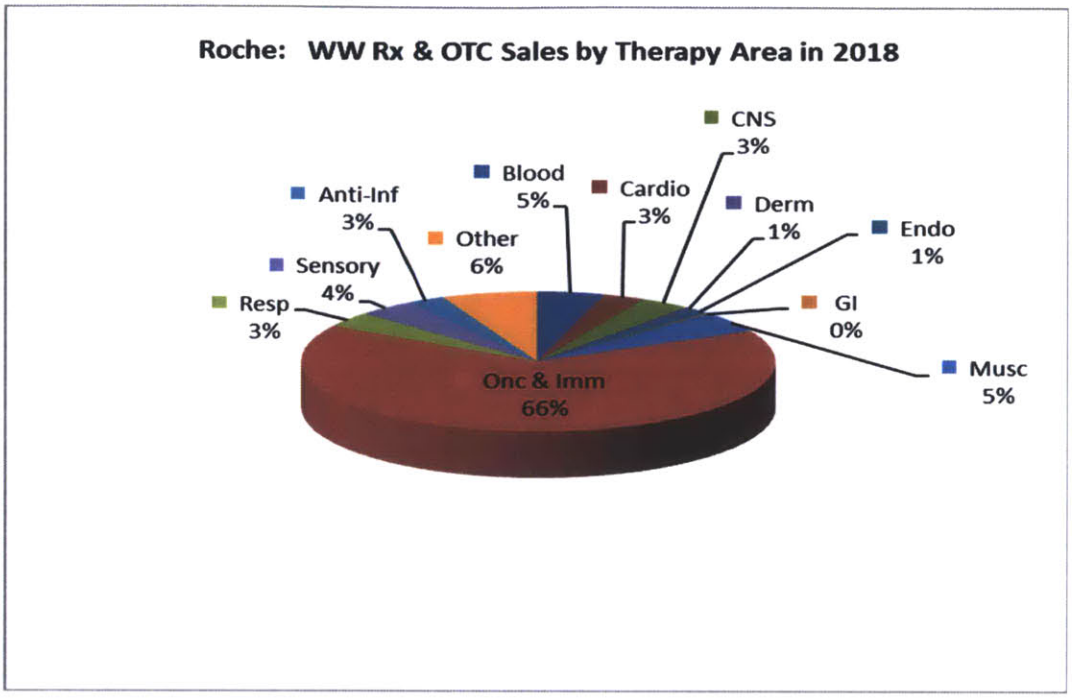


Fig. 3.18. Roche's projected sales by therapeutic area in 2018. *(Source: Evaluate Pharma).*

Chapter 4

In the previous chapters, I reviewed the key challenges faced by the global biopharmaceutical industry. I assessed the financial performance of the R&D investments made by ten of the biggest and most influential global biopharmaceutical companies in light of these challenges. In this chapter, I review the aftermath of the major changes in an industry that is going through what is perhaps the biggest transformation in its entire history. Unlike most other products and services that people consume, affordable healthcare and ready access to medicines that can change the course of a person's life are not optional. The global biopharmaceutical industry became one of the most profitable in the world, largely on the basis of a stable and lucrative financial framework upon which it was built. Willing risk takers in dynamic financial markets were able to underwrite very risky bets which paid off handsomely on a few occasions.

As I have demonstrated, much of this has changed forever. The combined forces of constrained markets, lower profitability due to restricted reimbursements, increased regulatory scrutiny and uncertainty, and a significantly lower appetite for risk has changed the business model of the biopharmaceutical industry.

This evolution brings with it new challenges and opportunities. Innovative business models are being proposed and implemented. For the first time in history, a much larger segment of the world's population is able to participate in making decisions that impact their health. The increasing economic might of sizeable populations in emerging economies like China and India is now a major factor in every decision that a global biopharmaceutical company.

As we have seen, each of the ten companies that I studied has come to realize that the age of the blockbuster drug is now over. Yet, shareholders of these companies still have expectations of returns that are now highly unlikely. The recent financial performance of each of the ten companies that I studied shows that profitability is on the decline. The entire

industry is in the process of retreating from the massive investments that defined the blockbuster era, with significant negative consequences for patients, shareholders, and employees. Tens of thousands of people have lost their jobs, and this trend is likely to continue for some time to come. The systemic impact of this phenomenon is likely to be felt for many years to come.

There is little doubt that the industry is unlikely to go back to the blockbuster era, or even create a financial encore in the post-blockbuster era. The real question is if the industry can survive at all in its present form. There is little if any consensus about what comes next. Each company has chosen a different strategic path as evidenced by the recent mergers, acquisitions, and divestitures. Some like AstraZeneca and Merck have chosen to continue with branded pharmaceuticals, hoping that the down cycle will eventually pass, and that by adding new therapeutic areas or becoming better at using technology they can continue to generate large profits from proprietary R&D that they own exclusively. Many others like Roche, Abbott, Pfizer and Amgen are becoming more diversified, and have expanded into such sectors as diagnostics, consumer health, generic drugs, biosimilars, nutrition, and wellness.

Industry experts agree on one thing – that there has never been a time in the industry where a more divergent approach to the future has existed. In the next decade and beyond, companies are unlikely to know what's going to happen. Indeed, it is becoming increasingly certain that they can't know what is likely to happen, because most of the rules under which they have operated for so long are changing in a fundamental way.

However, one thing is certain – none of the new areas of expansion that are open to the biopharmaceutical industry offer the same margins as branded drugs. The already declining levels of profitability of these companies are likely to continue, and those that cannot operate efficiently under these new rules will not survive, or at the very least, will struggle to remain independent. "Some will, some won't, because there won't be as big a proprietary market to go around in the near term," says Miles D. White, the chief executive of Abbott Laboratories,

which is in the process of separating into two companies, one focused on diagnostics and medical devices, the other on prescription drugs.

To survive — and perhaps thrive — in this unpredictable future, pharmaceutical companies need to make some bets about the way the future of the industry will unfold, and design their diversification strategies to position them for success in one or more of the possible scenarios that might occur.

In my view, the industry needs to evolve to a point where a "portfolio of portfolios" becomes the norm. Every aspect of a company's core strategy will need to be revisited, with a portfolio approach to the very strategy of a given company. This trend has already started – Joseph Jiminez, the CEO of Novartis recently stated that while Novartis is firm in its support of innovation driven drug development capabilities and a strong intellectual property regime in the pharmaceutical industry, it will also aggressively pursue a strong generics strategy which will allow Novartis to rapidly take off-patent drugs from its own portfolio and that of other companies and bring them to the generics market. With the scale, global reach, and the formidable capabilities of Novartis's generics arm Sandoz, this dual strategy of pursuing novel innovative drugs and generics simultaneously is a major shift in the industry. The recent acquisition of a leading Turkish generics pharmaceutical company Mustafa Nevzat by Amgen is another indication that this dual strategy might have significant merit. These *strategic bets* which complement a companies' core capabilities are likely to be significant a source of differentiation.

Companies will need to construct a portfolio of these "strategic bets" which span the entire spectrum of their operations – from early discovery through product launch and marketing. The benefits of diversification have been well established in the context of financial markets. Most well diversified investors and investment portfolio managers rarely rely on a single "tail event" – an event with an exceedingly low probability of success but with a disproportionately high return. Instead, they construct a portfolio of holdings that are constructed with a specific risk profile that is acceptable to the investors.

The construction of a portfolio of strategic bets is not intuitive, and faces significant opposition from the current cadre of senior executives in the biopharmaceutical industry, many of whom believe that there will be a revival of the old model of blockbuster drugs discovered, developed and marketed through big investments in the traditional R&D model. In this study, I have attempted to present evidence that this is unlikely.

I recommend that the industry would be better off by building such a portfolio of strategic bets by developing a set of adaptable business models which are optimized to provide better health outcomes to patients, lower risk to shareholders and employees, and are more likely to succeed in delivering new medicines in a more constrained and less predictable regulatory environment.

Identifying Unknowns

As paradoxical as this might sound, biopharmaceutical companies can do a much better job of assessing the unknowns that impact the industry. Much of the recent history of the industry has been based on the assumption that the process of discovering, developing, and marketing a new drug is a deterministic process. Collectively, the industry has followed a process of conducting a limited set of "experiments" to accomplish this objective. To a first order approximation, each of the ten companies I studied have followed the same strategy – focusing on a few disease areas and working through the painstaking process of building a proprietary pipeline of novel drugs, most of which would not make it to the market. In fact, the cumulative risk-adjusted probability of any molecule being successfully launched as a product is miniscule.

This is unsustainable in the future since many of the deterministic factors that I have outlined earlier – IP protection, high reimbursement, high profit margins, a predictable if slow regulatory path, and the relative patience of investors who viewed the biopharmaceutical companies as safe investments, have all changed in a fundamental way. So just how uncertain is this new era? Predicting how any one of these factors will evolve in the next decade is much more difficult, and the probability of being able to accurately predict the evolution and

interdependence of all of these factors is nearly impossible. The industry has moved from a deterministic era to a stochastic era, where most of the factors that will determine the success of the industry are inherently unpredictable.

This is not unique to the biopharmaceutical industry. Most industries go through periods of both deterministic and stochastic development. In the 1960s and 1970s, most of the prominent companies in the computer industry – IBM, Burroughs, Cray, and Digital Equipment Corporation – all followed a fairly well characterized, deterministic path. All these companies also followed similar strategies focused on mainframe computers. The advent of the personal computer changed the industry forever, and brought a swift end to the mainframe era. Burroughs, Cray, and DEC disappeared quickly, and IBM almost disappeared. It was the bold strategic shift embraced by Lou Gerstner that rescued IBM. Today, IBM is nothing like the company it was just twenty years ago. It follows a fundamentally different business model, and has created an enviable portfolio of strategic bets – a portfolio of portfolios – and has become incredibly good at executing on these strategic bets, enhancing those that work, and rapidly shedding those that do not work.

In this new, stochastic era of the biopharmaceutical industry each of the ten companies that I studied have very have divergent views of how the future will evolve. One measure of this is the fact that while there was massive consolidation through mergers and acquisitions, the M&A activity followed no clear pattern. Much of it was driven by a need to replace rapidly dwindling revenue streams brought upon by patent expirations, as in the case of Pfizer. Others, such as Merck acquired companies to bolster weak pipelines with the hope of succeeding under the old model of drug development.

Mergers and R&D alliances have been part of the life-sciences industry for a very long time. Since the mid-1990's, and particularly since the early 2000's, very large mergers between global pharmaceutical companies became much more commonplace. Almost every biopharmaceutical company that I studied is a product of one or more mergers – GSK, Novartis, Roche, Pfizer, Sanofi, Astra-Zeneca, etc. During the same period, R&D alliances were more

prevalent between large companies and small, targeted biotech companies and academia. Most of these R&D alliances were opportunistic rather than strategic, and were often driven by specific interests in a molecule, gene, pathway, or disease indication.

At an industry level, much of the M&A activity is viewed as not having succeeded in meeting the primary stated objective – improvement in R&D productivity and the efficiency and impact of the pipeline. An inevitable conclusion that can be derived from this is that M&A activity is an ineffective method of augmenting and de-risking a pipeline. This is supported by recent evidence, and is consistent with the views expressed by leading experts in the industry, including Mr. Ray Gilmartin who was the Chairman & CEO of Merck & Company until recently.

One area where M&A activity seems to hold promise is in biologics. Most of the companies I studied have rapidly built capabilities in biologics (also known as large molecule drugs), primarily through targeted acquisitions. Due to the higher barrier to entry, lower threat from biosimilars, and a relatively stable reimbursement horizon, biologics offer much needed diversification, and have become an important component in the portfolio of strategic bets of each of the companies I studied.

Another important element in this diversified portfolio of strategic bets is M&A activity directed at market expansion and internationalization, reducing the cost of logistics, operations, manufacturing, and in attaining a better bargaining position with increasingly powerful payers.

R&D alliances, on the other hand can have substantial positive impact on R&D productivity. In my view, a diverse portfolio of globally sourced R&D alliances can be an effective strategic bet for a fraction of the costs associated with M&A activity. These alliances often provide a diversity of thought and ideas, and perhaps most importantly, can align the incentives of the internal R&D staff and the alliance partners around achieving quantifiable success in a defined time period.

The Value of Strategic Bets

These attempts at diversification – M&A, R&D alliances etc. – are unlikely to solve the core problems of the biopharmaceutical industry. Although it might appear that these strategies are designed to position a company for success in one or more of the business scenarios that are likely to occur, most management teams are unable to predict with any degree of certainty as to which specific business scenario is more likely to occur – there are too many unknowns. Even those companies that have systematically acquired capabilities that seem to hedge against one or more of the unknowns face an uncertain future.

Most of the companies that I studied appear to be adding new businesses primarily to expand their portfolios and reduce the volatility of revenue and earnings. In an industry defined by long product development cycles and extreme costs, focusing on quarterly earnings and near-term revenue growth is no longer sufficient. For example, J&J has built a portfolio of healthcare companies, many of which were acquired in the last decade. The view of the top management team at J&J is that each of these portfolio companies must survive and become profitable independently.

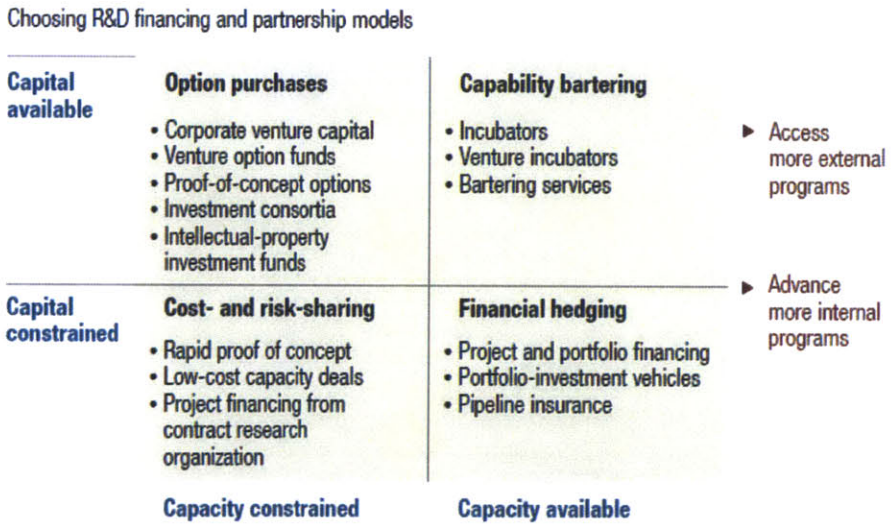


Fig. 4.1. A Capacity Vs. Capital model for selecting a portfolio of strategic bets in the biopharmaceutical industry. *(Source: Eric David et al, McKinsey & Company)*

This mind-set of building a diverse portfolio of related companies as in the case of J&J, is fairly common in the biopharmaceutical industry. The underlying assumption is that these quasi-independent companies should be managed separately, and their individual profits maximized. While this strategy might have made good sense in a deterministic environment, recent evidence suggests that it is less likely to succeed in a stochastic environment. These businesses are inherently correlated and are exposed to many of the risk factors I have described previously. In a healthcare environment defined by unknowns in which no company can realistically predict how the future will evolve, this approach of building a portfolio of stand-alone companies is insufficient.

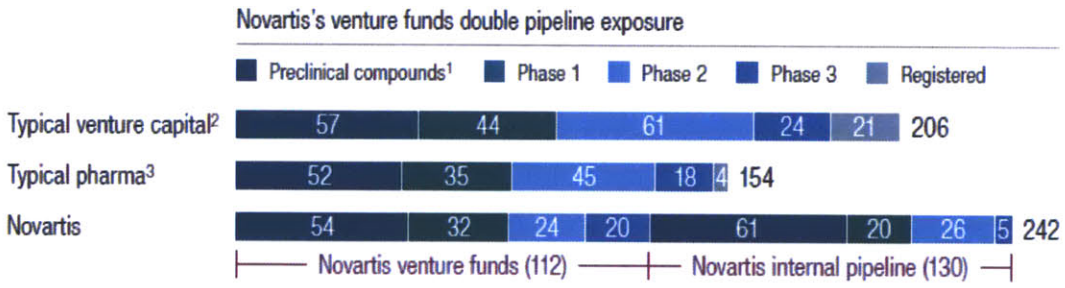
The announcement by Abbott Labs to separate into two independent, publically traded companies signals the industry's acceptance of this fact. By splitting into two companies – a medical products company, and a research-based biopharmaceutical company - Abbott is shielding the less profitable but more predictable medical products business from the more risky research-based pharmaceuticals business. This is good for Abbott's shareholders – they will realize the value created by Abbott's integrated strategy of the past, but are free to decide if they wish to participate in the stochastic future of Abbott's pharmaceutical business.

This approach of building a portfolio of strategic bets may provide the companies that I studied with greater flexibility in adapting their market positions, operating models, geographical footprint, and regulatory exposure. In an increasingly stochastic environment, the ability to rapidly reallocate scarce resources in order to maximize value and minimize risk will prove to be an important differentiator.

Some companies like Novartis have already made significant progress in this direction. Most notably, Novartis's relentless drive to build a portfolio of products that can weather the current environment is a remarkable achievement. For example, even at over $6 billion in annual revenue, Novartis's best-selling anti-hypertensive drug Diovan only makes up about 12% of its overall revenue. Thus, when this product comes off patent in 2012, the revenue shock to Novartis will be less significant than that faced by other companies. Even more remarkable is

the fact that in the case of Diovan, Novartis has a credible plan to retain over 50% of the revenue after patent expiry – nearly $3 billion in perpetuity - by expanding the market for Diovan into the increasingly lucrative Chinese and Indian markets. Novartis will also remain in firm control of the global supply of Diovan by ensuring that most of the manufacturing of generic Diovan is done by Novartis's generics arm, Sandoz.

In the previous chapter, I showed that Novartis was the only company amongst its peers to have a positive NPV on its R&D investments between 2007 and 2011. This was primarily due to its ability to place multiple strategic bets – cost reduction, expansion into generics, emerging markets, biologics, biosimilars, stratified medicine, and most notably – a shift away from the blockbuster paradigm. The diverse portfolio of drugs that are in Novartis's current pipeline address a range of unmet medical needs in developed and emerging markets, with many of these potential drugs likely to have peak sales of well under $1 billion.



[1]Based on estimated completeness of sources. The issue is that some of the preclinical data is not completely reliable.
[2]Average of 3 of the most active pharma venture funds.
[3]Average of 3 of the top pharma companies, by revenues.
Source: Capital IQ; EvaluatePharma database; Novartis Venture Fund 2005 Activity Report; portfolio company Web sites

Fig. 4.2. Novartis's approach to building a diversified pipeline.

Another hypothesis that is gaining momentum is that in the near future, disease management will have less to do with prescription drugs and physician intervention, and will increasingly become the responsibility of the patients. In this scenario, companies are likely to enhance their portfolio of options by expanding into the consumer healthcare business. If this scenario gains traction, the company will already have the platform in place to make its overall business more successful by successfully combining pharmaceuticals with consumer health. If

however, this scenario does not gain traction in a reasonable time period, the company making the strategic bet can alter its treatment of the unit by managing it for profit or selling it off.

Another likely scenario is that diagnostics will become essential in ensuring the success of most drugs in the future by identifying patients who are most likely to benefit from a particular drug. In a world where an increasing number of reimbursement decisions are based on the effectiveness of a drug, the ability to find and treat patients who can truly benefit form a drug will offer an important competitive advantage. The combination of proprietary diagnostics and effective drugs is likely to improve the effectiveness of the R&D investments of these companies and will contribute significantly to improved profitability.

The construction of an effective portfolio of strategic bets should become the highest priority of the senior management of biopharmaceutical companies. In my view, this effort should be led by the CEO, and should include the top management team of a company. It is likely that in almost all cases, this process will change the strategic direction of the company. The compensation packages of the CEO and the top management team of these companies must primarily be based on the contextual validity of such a portfolio of strategic bets in an increasingly stochastic environment, and less on quarterly earnings and near-term financial performance of these companies.

In a recent study on CEO compensation, McKinsey & Company concluded that long-term value creation should become a major component of guiding CEO compensation. This is increasingly true for the biopharmaceutical industry, where a key measure of performance is the recognition that long-term value creation is a function of returns on capital, sustainable growth, and predictable cash flows. However, establishing a performance-based compensation system for the CEOs and other senior executives in a biopharmaceutical company is not an easy task. The special skills required to navigate an inherently long-cycle industry through a turbulent period defined by unknown risks are not easy to find and retain.

To date, most companies continue to reward CEOs and the senior management team for short-term total returns to shareholders. Short-term returns are driven more by systemic

changes in the industry and movements in the broader market than by individual performance. Thus, stock-option based compensation for senior executives in publically traded biopharmaceutical companies might be inappropriate in the stochastic era that is now the reality for this industry. Instead, a compensation system based on sustainable growth by successfully executing on strategic bets, returns on investments (R&D in particular), and performance relative to peers is likely to be more impactful.

CEO compensation in the biopharmaceutical industry has come under greater scrutiny in recent years, largely due to the fact that some of the core principles of finance have been ignored by the industry. Sustainable value creation in a stochastic environment is incredibly hard, and employing the techniques that have succeeded in past, or in other industries is not likely to be successful. It is not surprising that the spate of M&A activity, share buy-backs, reductions in staffing, externalization of R&D and other operations to take advantage of cost arbitrage, etc. have not succeeded. In the book "Value: The Four Cornerstones of Corporate Finance", Richard Dobbs and his co-authors argue that creation of long-term value for shareholders and society at large can only be accomplished by a more thoughtful application of the basic principles.

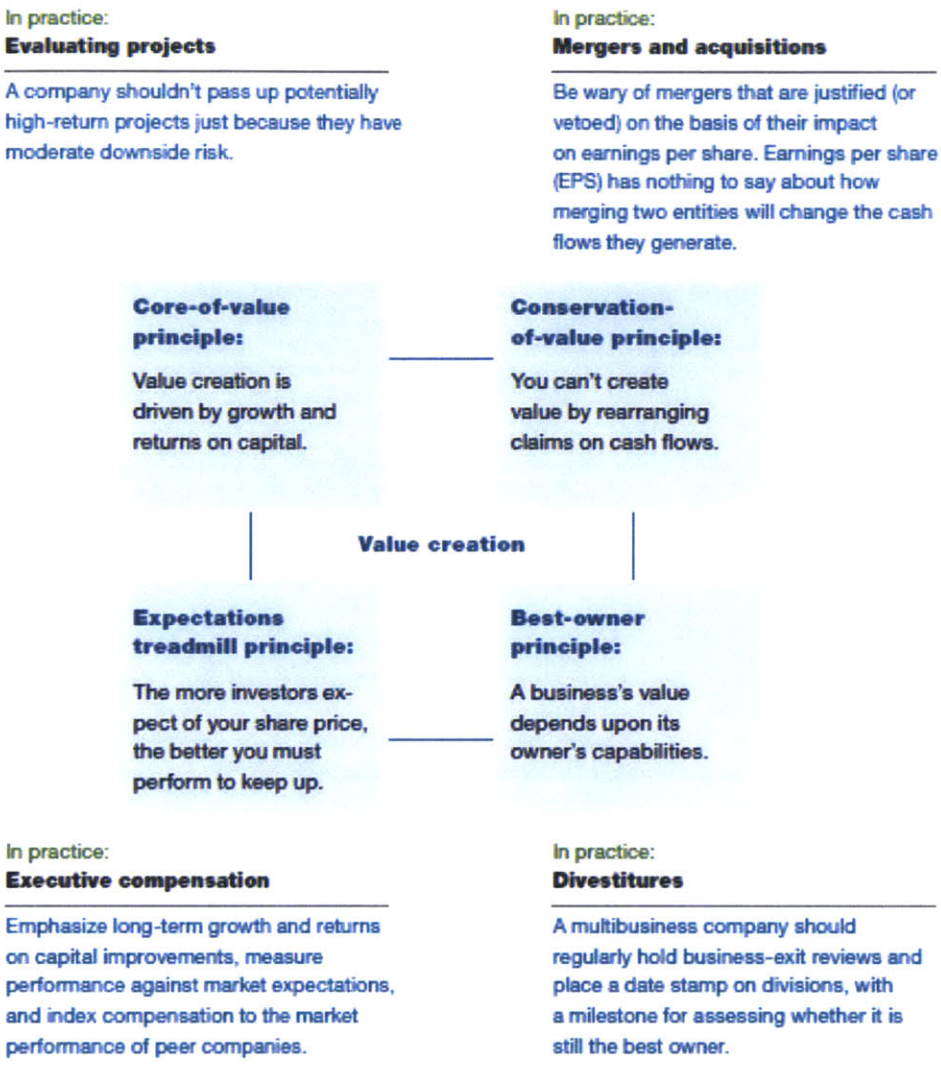


Fig. 4.3. The Four Cornerstones of Corporate Finance. (*Source: "Value: The Four Cornerstones of Corporate Finance" by Richard Hobbs, Bill Huyett, and Tom Koller (Wiley, October 2010)*

Conclusions & Recommendations

Much of this work has been focused on understanding the drivers for the poor outcomes for R&D investments in the biopharmaceutical industry. With few exceptions, each of the ten companies that I studied has faced the same set of challenges in transitioning form a deterministic environment to a stochastic environment. Changes in reimbursement, the

evolution of the regulatory landscape, and the passing of the blockbuster era have led to increasing uncertainty for the biopharmaceutical industry. One approach to improving the performance of the industry is based on the application of a "portfolio of portfolios" methodology to the discovery and development of medically relevant and financially successful drugs.

Even as we consider a portfolio based approach, it is important to recognize that several unknown and unquantifiable risks remain. Companies that are most likely to succeed in the future will be those that can successfully fine-tune the risk-reward profile within segments of a portfolio – a portfolio of diseases from oncology to rare diseases, a portfolio of projects in the pipeline, a portfolio of strategic bets, or a portfolio of companies – with the ultimate goal of responding nimbly to market opportunities or perceived price-value gaps. However, it is important to recognize that while these efforts can help streamline a company by better allocation of capital and resources, R&D productivity will only be enhanced if they can consistently deliver additional successful programs at lower cost and reduced risk.

The application of portfolio theory to reducing the risk and improving the productivity of R&D investments whether in the private sector, or in government funded research has significant merit. This approach would lead to greater transparency, improved objectivity, and better and more reproducible outcomes from the extraordinary R&D investments made by the biopharmaceutical industry. Ultimately, a "portfolio of portfolios" would also have to consider the societal implications of developing drugs for not just mainstream diseases that impact millions of people in the developed and emerging markets, but also rare diseases that impact small numbers of patients. If successfully applied, an efficient "portfolio of portfolios" would not only provide substantial returns to shareholders, but would also improve the lives of patients everywhere. My work suggests that the following five principles are likely to define the biopharmaceutical industry in the next decade and beyond.

Changes in the industry are inevitable and permanent: The era of the blockbuster model and the reliance on proprietary, internally developed R&D capabilities are at an end. Companies

that accept this reality at the highest levels of management, and consider adopting a portfolio of strategic bets are likely to emerge stronger in the next decade.

Consider a range of future scenarios and accept the fact that many unknowns remain: Although we are entering a stochastic period in the biopharmaceutical industry, it does not mean that every outcome is equally possible. A continuous evaluation of the possible outcomes and proactive engagement with payers, regulators, potential partners, and investors can help companies develop options on how they would respond to any given scenario.

Assess the inherent capabilities of the company: Identifying and enhancing the core capabilities that differentiate a company is particularly important during a period of big change. It is unlikely that many of the capabilities that made the companies I studied successful in the past are likely to be factors in their future success. For example, while Novartis is well underway in executing on many of the strategic bets that are likely to have a positive impact in the future, many of the other companies such as Merck & Company and AstraZeneca are just beginning this process.

Identify those strategic bets that can enhance a company's leadership position: Traditional biopharmaceutical companies such as AstraZeneca or Amgen are unlikely to transform into a diagnostics leader in a reasonable time. Established leaders such as Roche and J&J are likely strengthen their leadership position in diagnostics. However, AstraZeneca and Amgen can create strategic partnerships with diagnostics companies as part of a "portfolio of partners". The same logic applies to adding a generics capability, where a company like Novartis is a dominant player. Pfizer's strategic investment in strengthening its generics arm, Greenstone is an indication of Pfizer's intent to execute on a strategic bet in generics.

Align the corporation at every level to execute effectively on strategic bets: From the CEO and senior management team to the R&D scientist in the lab, ensure that there is a clear alignment with the concept of a portfolio of portfolios. The success of any strategic bet will depend largely on speedy and effective execution. This is particularly true in R&D, where even small changes in direction take years to implement.

Companies that succeed in the future will recognize that while this stochastic period might last for the foreseeable future, stability will eventually return. While some unknowns might persist, there is likely to be more harmonization and predictability in the regulatory landscape. Reimbursement strategies and the impact of payers are also evolving, and while it is clear that industry will not be as profitable as it once was, revenue streams are likely to become more predictable. The emergence of countries like China and India as leading consumers of healthcare will also change the revenue horizon in a positive direction.

Each of the ten companies I studied has a very different approach on how to navigate the turbulent times that face the industry. This portfolio of strategies offers an opportunity for the industry to experiment with their own set of strategic bets, strengthening those that work and rapidly abandoning those that do not.

Suggestions for future work

In this study I have taken a qualitative approach to assessing the paradox of declining R&D productivity in the face of massive R&D investments by the industry, particularly in the last decade. Each of the ten companies I studied has faced major challenges, and only one – Novartis – has bucked this trend of lower R&D productivity. Novartis was early to recognize the fundamental shifts in the industry, and implemented a portfolio approach to not just its R&D pipeline, but to a series of strategic bets that it continues to refine. I propose that future work should be aimed at understanding the evolving landscape from three related yet distinct perspectives:

- A formal, quantitative approach to assessing the risk to reward ratio of a selected set of well-defined strategic bets. Drawing from established principles in finance theory, such a study would attempt to quantify the magnitude and duration of a set of investments in R&D and related areas in the face of unknown and unquantifiable risks.
- A quantitative assessment of the impact of a diversified portfolio of strategic bets on the financial performance of companies. For instance, would an Innovative Pharma +

Diagnostics company provide better returns to shareholders than an Innovative Pharma + generics company? What would the impact of rare diseases and orphan drugs be on a Pharma company that has focused primarily on mainstream diseases? What is the quantifiable impact of a reimbursement model that is not based on the single-payer or third-party payer system?

- A quantitative approach to developing a model for constructing a "portfolio of portfolios" – R&D pipelines, investment choices (venture capital, private equity, disease specific funds, pipeline insurance), disease areas (therapeutic area, mainstream diseases Vs. rare diseases), manufacturing capacity, regulatory risk, etc.

Appendix A

***NOTE**: All financial data in this Appendix was obtained from the company specific "S&P Compustat Company Report".*

Selected Financial Data: Abbott Laboratories

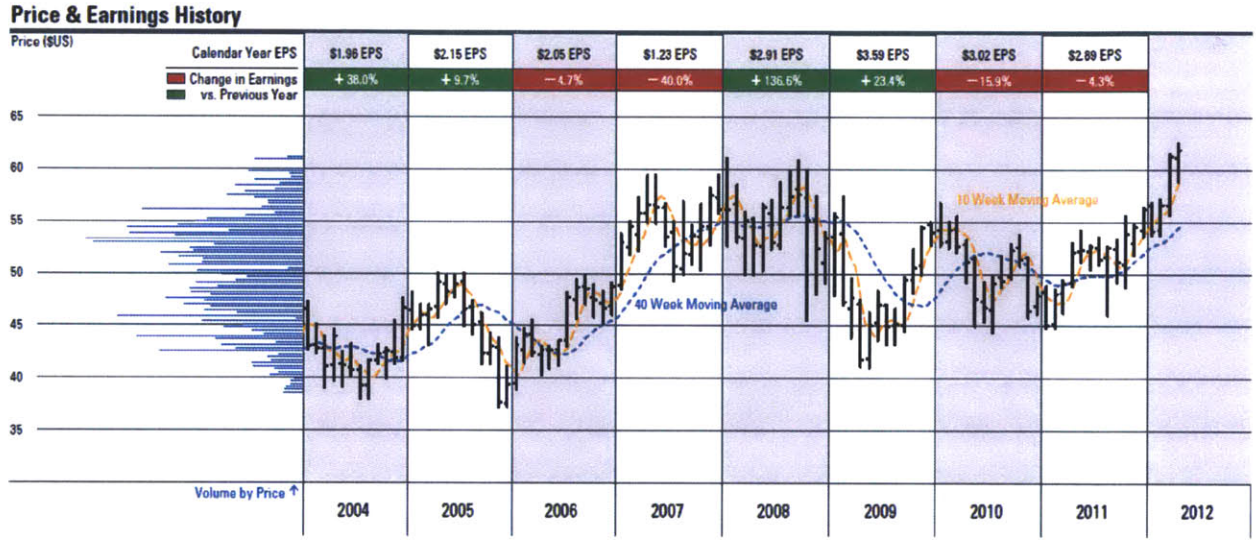


Fig. A.1. Abbott Laboratories (ABT) price and earnings history as a function of its stock price (2004 – 2012).

Table A.1. Abbott Laboratories key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	23.1x	18.3x	43.5x	24.3x	17.6x	14.6x	16.2x	18.7x	--
Price/Sales	3.7x	2.7x	3.3x	3.4x	2.8x	2.7x	2.1x	2.3x	--
Price/Book Value	5.1x	4.2x	5.3x	4.9x	4.7x	3.7x	3.3x	3.6x	--
Price/Cash Flow	16.3x	12.8x	22.9x	15.9x	12.6x	10.7x	10.2x	11.4x	--
Gross Margin	62.1%	59.6%	65.5%	65.1%	64.7%	64.8%	67.6%	68.7%	--
Profit Margin	16.1%	15.1%	7.6%	13.9%	16.0%	18.7%	13.2%	12.2%	--
Sales/Employee	$324.8 Th	$373.1 Th	$337.2 Th	$381.1 Th	$427.9 Th	$421.4 Th	$390.7 Th	$426.9 Th	--
Income/Employee	$52.4 Th	$56.5 Th	$25.8 Th	$53.0 Th	$68.6 Th	$78.7 Th	$51.4 Th	$52.0 Th	--
Return on Equity	22.2%	23.4%	12.2%	20.3%	27.1%	25.1%	20.7%	19.3%	--
Return on Assets	11.0%	11.6%	4.7%	9.1%	11.2%	11.0%	7.8%	7.8%	--
PEG (Historical Growth)	0.9x	2.7x	-3.1x	5.3x	1.5x	0.3x	1.9x	-84.7x	--
Beta	0.2	0.2	0.4	0.3	0.2	0.2	0.3	0.3	--
Annual Dividend	$1.04	$1.11	$1.18	$1.30	$1.44	$1.60	$1.77	$1.92	--
Dividend Yield	2.2%	2.8%	2.4%	2.3%	2.6%	2.9%	3.6%	3.3%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

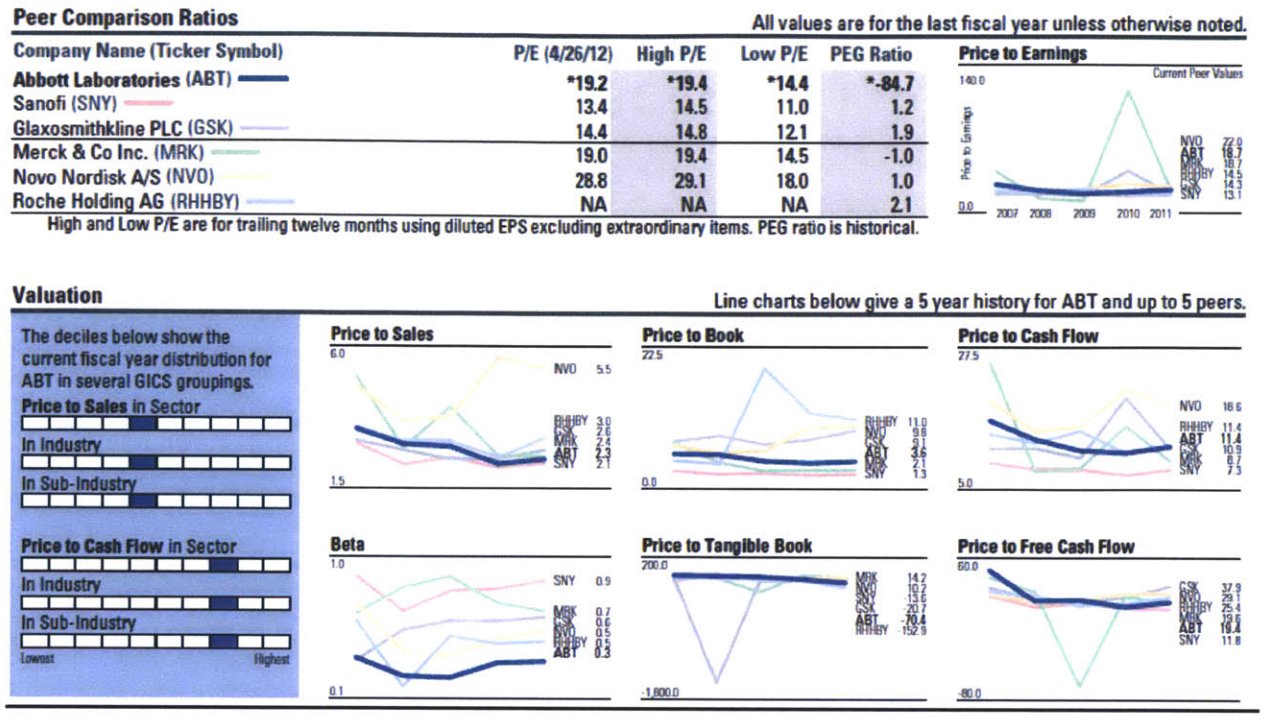


Fig. A.2. Abbott Laboratories company performance in comparison to its industry segment (2004 – 2012).

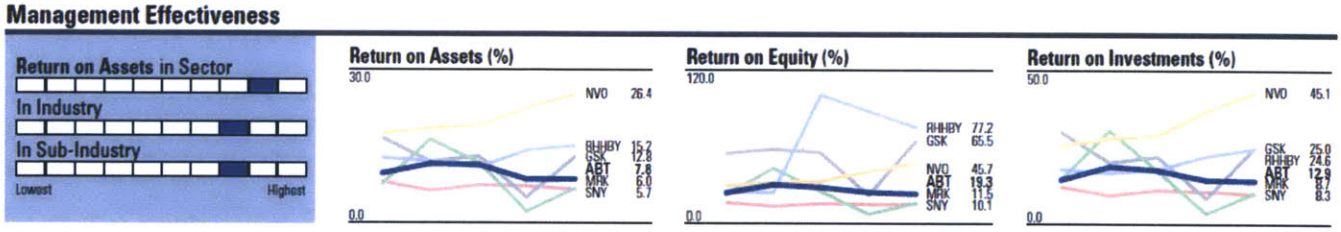


Fig. A.3. Management effectiveness of Abbott Laboratories in comparison to selected peers in its industry segment.

Selected Financial Data: Amgen, Inc.

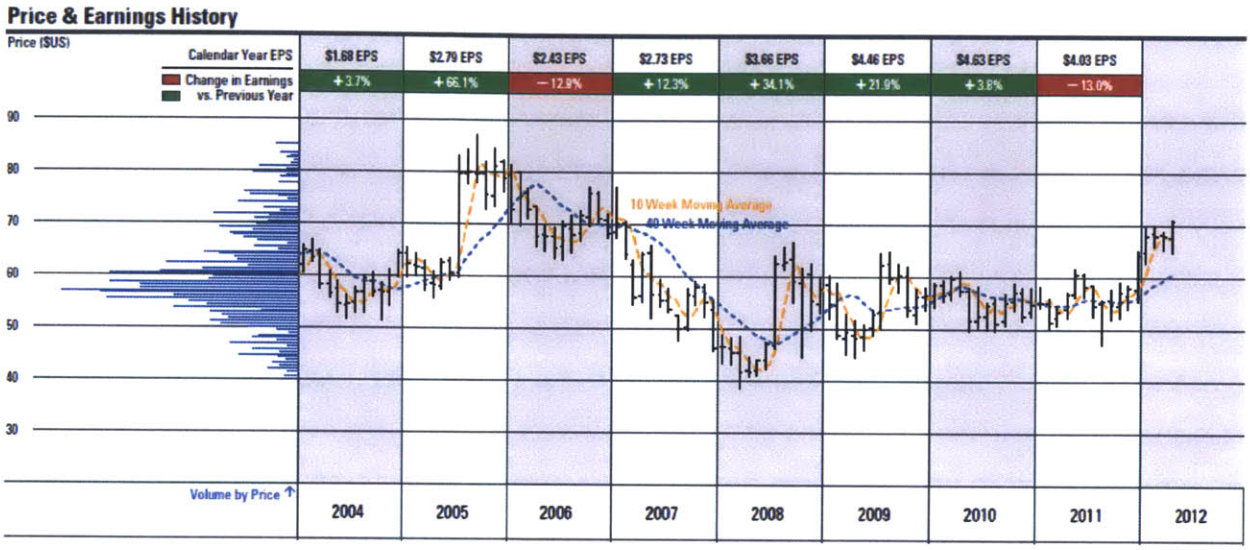


Fig. A.4. Amgen (AMGN) price and earnings history as a function of its stock price (2004 – 2012).

Table A.2. Amgen's key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	35.4x	26.9x	27.5x	16.5x	14.8x	12.5x	11.5x	15.9x	--
Price/Sales	7.7x	7.8x	5.6x	3.4x	4.0x	3.8x	3.4x	3.3x	--
Price/Book Value	4.1x	4.7x	4.2x	2.8x	3.0x	2.5x	2.1x	2.7x	--
Price/Cash Flow	26.1x	21.4x	20.4x	11.6x	11.5x	10.0x	9.1x	10.8x	--
Gross Margin	87.4%	87.6%	89.8%	90.7%	90.5%	90.9%	90.1%	89.8%	--
Profit Margin	22.4%	29.6%	20.7%	21.4%	28.0%	31.5%	30.7%	23.6%	--
Sales/Employee	$732.6 Th	$753.3 Th	$709.9 Th	$844.1 Th	$887.8 Th	$851.3 Th	$865.1 Th	$875.4 Th	--
Income/Employee	$164.1 Th	$222.7 Th	$146.8 Th	$180.9 Th	$248.3 Th	$267.7 Th	$265.9 Th	$206.9 Th	--
Return on Equity	12.0%	18.0%	15.6%	17.7%	20.6%	20.3%	19.3%	19.4%	--
Return on Assets	8.1%	12.5%	8.7%	9.1%	11.5%	11.6%	10.6%	7.5%	--
PEG (Historical Growth)	1.7x	0.8x	2.0x	1.0x	1.5x	0.6x	0.6x	13.4x	--
Beta	0.5	0.8	0.7	1.1	0.4	0.5	0.5	0.4	--
Annual Dividend	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.00	$0.99	--
Dividend Yield	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.9%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

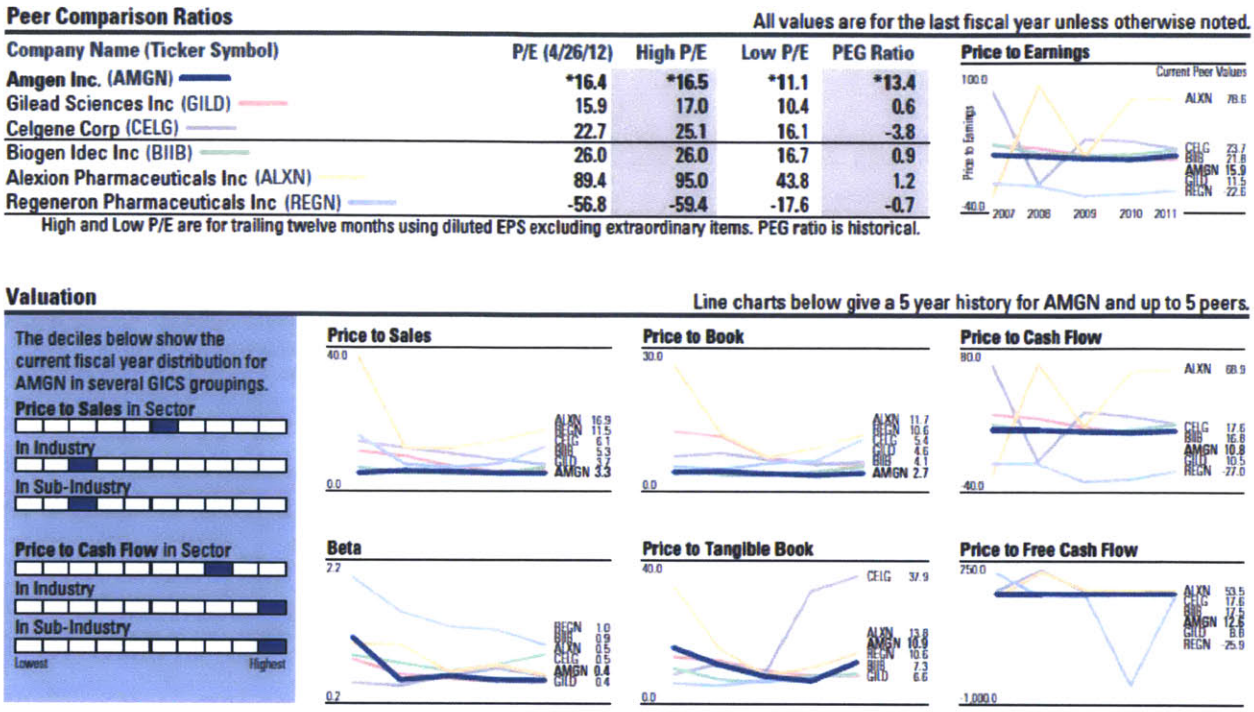


Fig. A.5. Amgen: company performance in comparison to its industry segment (2004 – 2012).

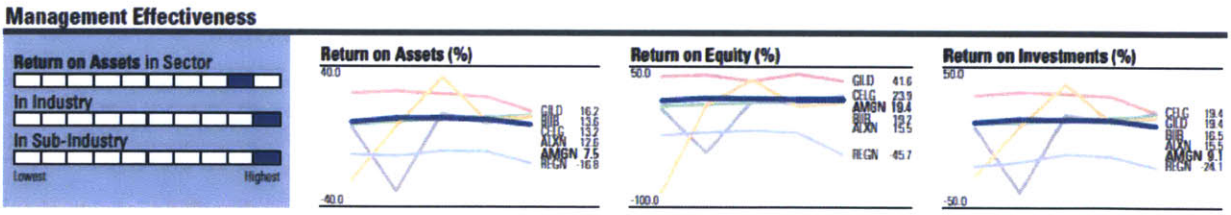


Fig. A.6. Management effectiveness of Amgen in comparison to selected peers in its industry segment.

Selected Financial Data: Astra Zeneca

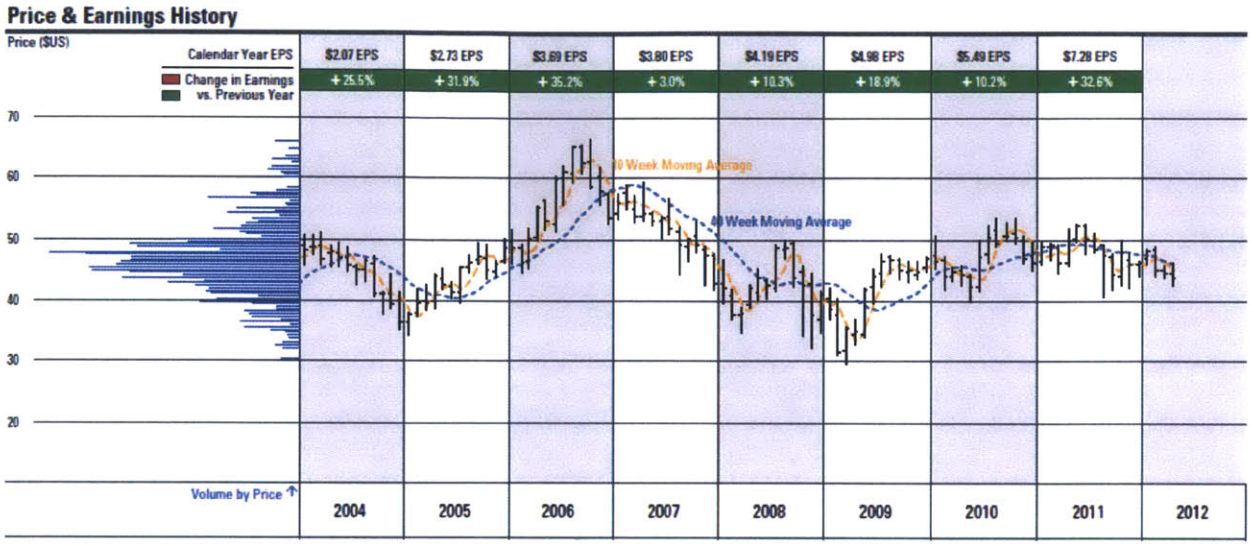


Fig. A.7. AstraZeneca (AZN) price and earnings history as a function of its stock price (2004 – 2012).

Table A.3. AstraZeneca's key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	16.0x	16.7x	13.9x	11.5x	9.8x	9.0x	8.3x	6.3x	--
Price/Sales	2.8x	3.2x	3.0x	2.1x	1.8x	2.1x	1.9x	1.7x	--
Price/Book Value	4.2x	5.7x	5.4x	4.2x	3.7x	3.3x	2.8x	2.6x	--
Price/Cash Flow	11.9x	12.9x	11.2x	8.6x	7.5x	7.4x	6.5x	5.0x	--
Gross Margin	82.0%	82.1%	84.1%	85.6%	86.6%	88.1%	87.2%	88.1%	--
Profit Margin	17.5%	19.5%	22.4%	18.5%	18.9%	22.7%	23.7%	29.0%	--
Sales/Employee	$338.6 Th	$369.7 Th	$404.2 Th	$449.1 Th	$495.6 Th	$519.4 Th	$550.7 Th	$574.7 Th	--
Income/Employee	$59.4 Th	$72.1 Th	$90.5 Th	$83.0 Th	$93.9 Th	$117.7 Th	$130.5 Th	$166.9 Th	--
Return on Equity	26.4%	34.6%	39.5%	37.9%	38.3%	36.4%	34.7%	42.9%	--
Return on Assets	14.9%	18.9%	20.2%	11.7%	13.0%	13.7%	14.3%	18.9%	--
PEG (Historical Growth)	1.5x	0.8x	0.5x	0.6x	0.8x	0.9x	0.6x	0.3x	--
Beta	0.5	0.4	0.7	0.6	0.4	0.7	0.6	0.6	--
Annual Dividend	$0.95	$1.06	$1.45	$1.82	$1.91	$2.09	$2.48	$2.90	--
Dividend Yield	2.3%	2.1%	2.6%	4.1%	4.6%	4.5%	5.2%	5.8%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

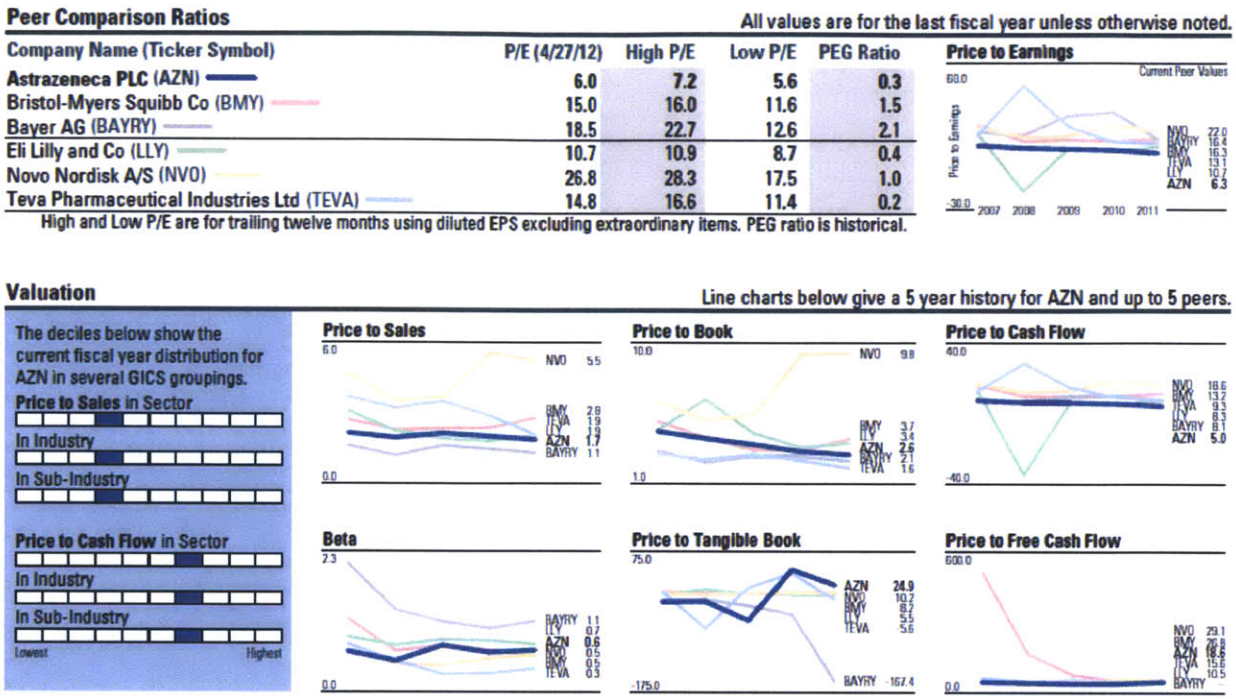


Fig. A.8. AstraZeneca: company performance in comparison to its industry segment (2004 – 2012).

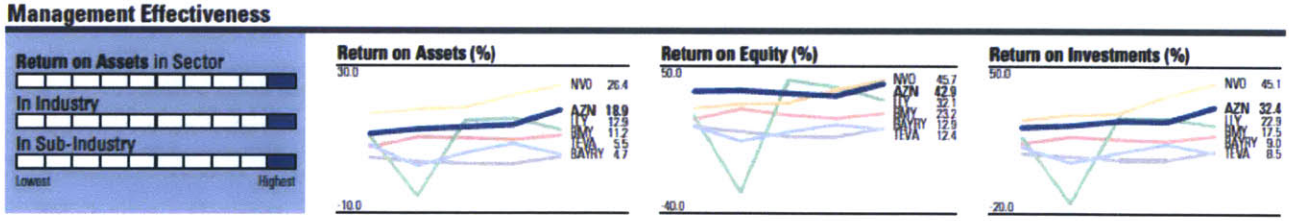


Fig. A.9. Management effectiveness of AstraZeneca in comparison to selected peers in its industry segment.

Selected Financial Data: Eli Lilly & Company

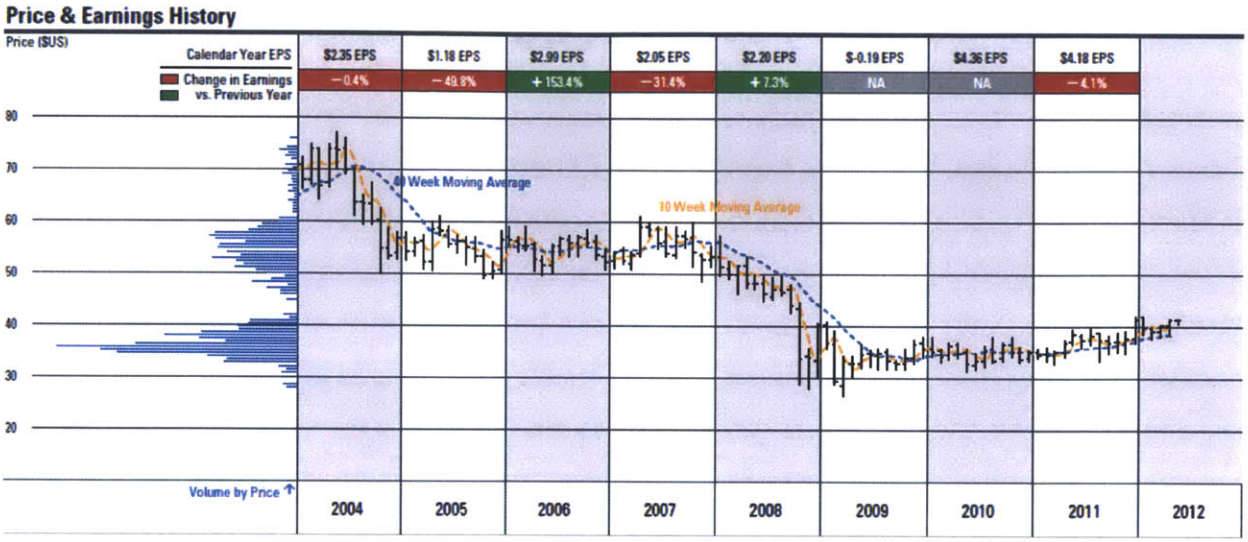


Fig. A.10. Eli Lilly (LLY) price and earnings history as a function of its stock price (2004 – 2012).

Table A.4. Eli Lilly's key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	34.2x	30.9x	21.3x	19.7x	-21.3x	9.1x	7.7x	10.7x	--
Price/Sales	4.5x	4.2x	3.6x	3.1x	2.2x	1.8x	1.7x	1.9x	--
Price/Book Value	5.7x	5.7x	5.2x	4.3x	6.6x	4.1x	3.1x	3.4x	--
Price/Cash Flow	26.9x	23.9x	17.3x	15.3x	-38.5x	7.2x	6.2x	8.3x	--
Gross Margin	80.3%	80.2%	81.4%	81.8%	83.3%	85.5%	86.0%	84.1%	--
Profit Margin	13.1%	13.7%	17.0%	15.8%	-10.2%	19.8%	22.0%	17.9%	--
Sales/Employee	$311.4 Th	$343.8 Th	$378.1 Th	$459.0 Th	$503.8 Th	$541.0 Th	$601.7 Th	$637.8 Th	--
Income/Employee	$40.7 Th	$47.0 Th	$64.2 Th	$72.7 Th	-$51.2 Th	$107.3 Th	$132.2 Th	$114.2 Th	--
Return on Equity	16.6%	18.5%	24.2%	21.9%	-30.8%	45.5%	40.8%	32.1%	--
Return on Assets	7.3%	8.1%	12.1%	11.0%	-7.1%	15.8%	16.4%	12.9%	--
PEG (Historical Growth)	-2.5x	-3.1x	19.1x	1.1x	-19.7x	0.5x	0.4x	0.4x	--
Beta	0.4	0.7	0.8	0.9	0.7	0.8	0.8	0.7	--
Annual Dividend	$1.42	$1.54	$1.62	$1.74	$1.90	$1.96	$1.97	$1.97	--
Dividend Yield	2.5%	2.7%	3.1%	3.2%	4.7%	5.5%	5.6%	4.7%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

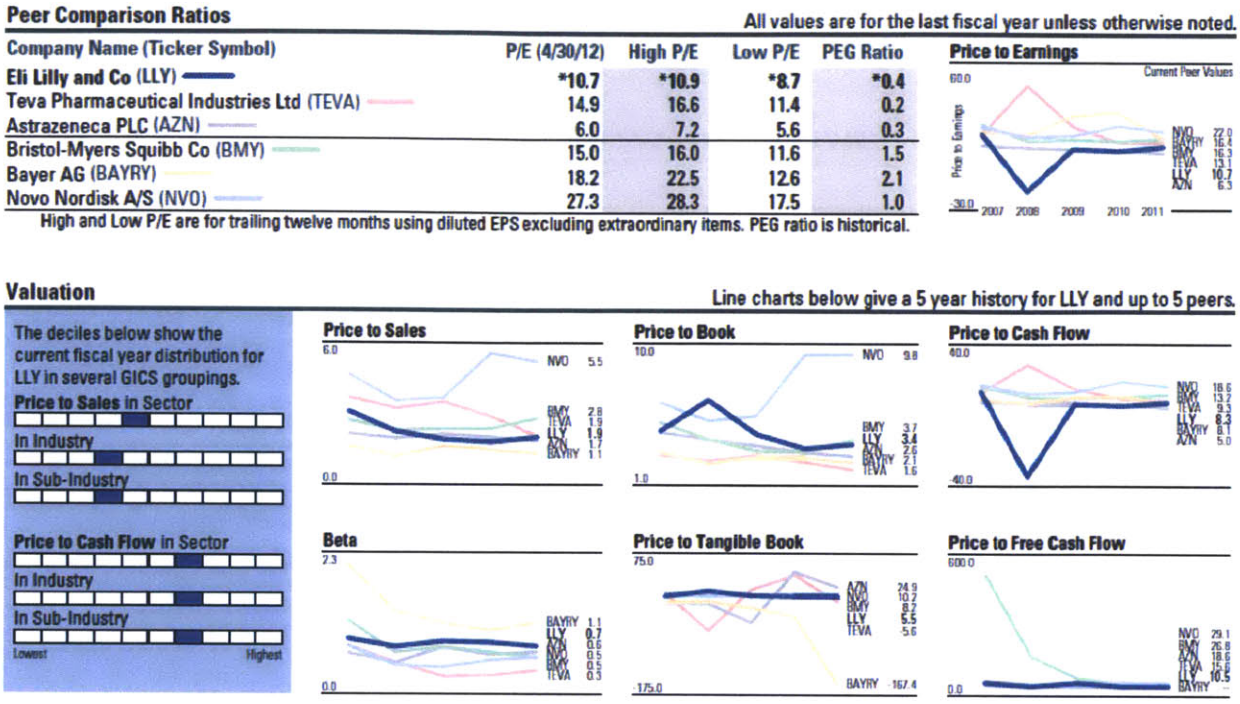


Fig. A.11. Eli Lilly: company performance in comparison to its industry segment (2004 – 2012).

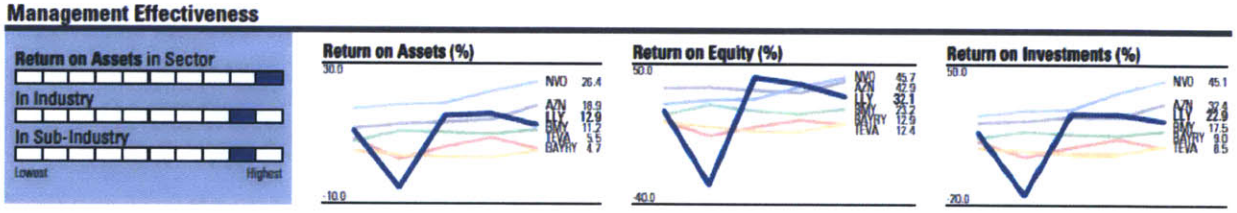


Fig. A.12. Management effectiveness of Eli Lilly in comparison to selected peers in its industry segment.

Selected Financial Data: GlaxoSmithKline

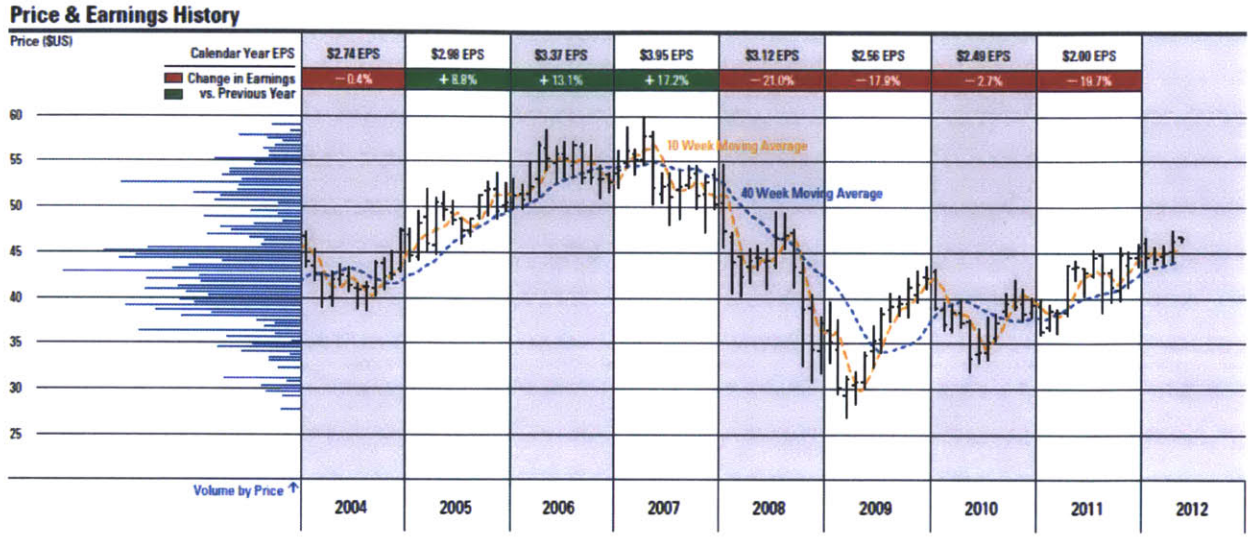


Fig. A.13. GlaxoSmithKline (GSK) price and earnings history as a function of its stock price (2004 – 2012).

Table A.5. GlaxoSmithKline (GSK) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	16.5x	17.9x	14.3x	13.6x	14.5x	12.1x	39.6x	14.3x	--
Price/Sales	3.4x	3.8x	3.2x	2.9x	2.6x	2.3x	2.3x	2.6x	--
Price/Book Value	11.9x	11.0x	7.8x	7.1x	8.1x	6.6x	7.4x	9.1x	--
Price/Cash Flow	13.6x	14.8x	11.9x	10.9x	11.1x	9.3x	20.0x	10.9x	--
Gross Margin	83.3%	82.5%	82.5%	82.0%	81.7%	81.0%	80.2%	79.2%	--
Profit Margin	21.0%	21.3%	22.9%	22.5%	18.5%	19.0%	5.7%	18.8%	--
Sales/Employee	$392.6 Th	$380.4 Th	$452.7 Th	$445.0 Th	$359.8 Th	$471.3 Th	$460.9 Th	$446.7 Th	--
Income/Employee	$82.6 Th	$81.0 Th	$103.7 Th	$100.1 Th	$66.5 Th	$89.5 Th	$26.1 Th	$83.9 Th	--
Return on Equity	72.6%	61.9%	55.9%	54.3%	58.0%	55.3%	18.4%	65.5%	--
Return on Assets	19.1%	17.2%	21.1%	16.8%	11.7%	12.9%	3.9%	12.8%	--
PEG (Historical Growth)	0.6x	1.8x	1.4x	1.5x	-4.8x	-6.6x	-1.1x	1.9x	--
Beta	0.2	0.1	0.2	0.3	0.5	0.6	0.6	0.6	--
Annual Dividend	$1.62	$1.52	$1.88	$2.15	$1.71	$1.97	$1.96	$2.36	--
Dividend Yield	3.4%	3.0%	3.3%	4.1%	5.7%	4.4%	5.1%	4.8%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

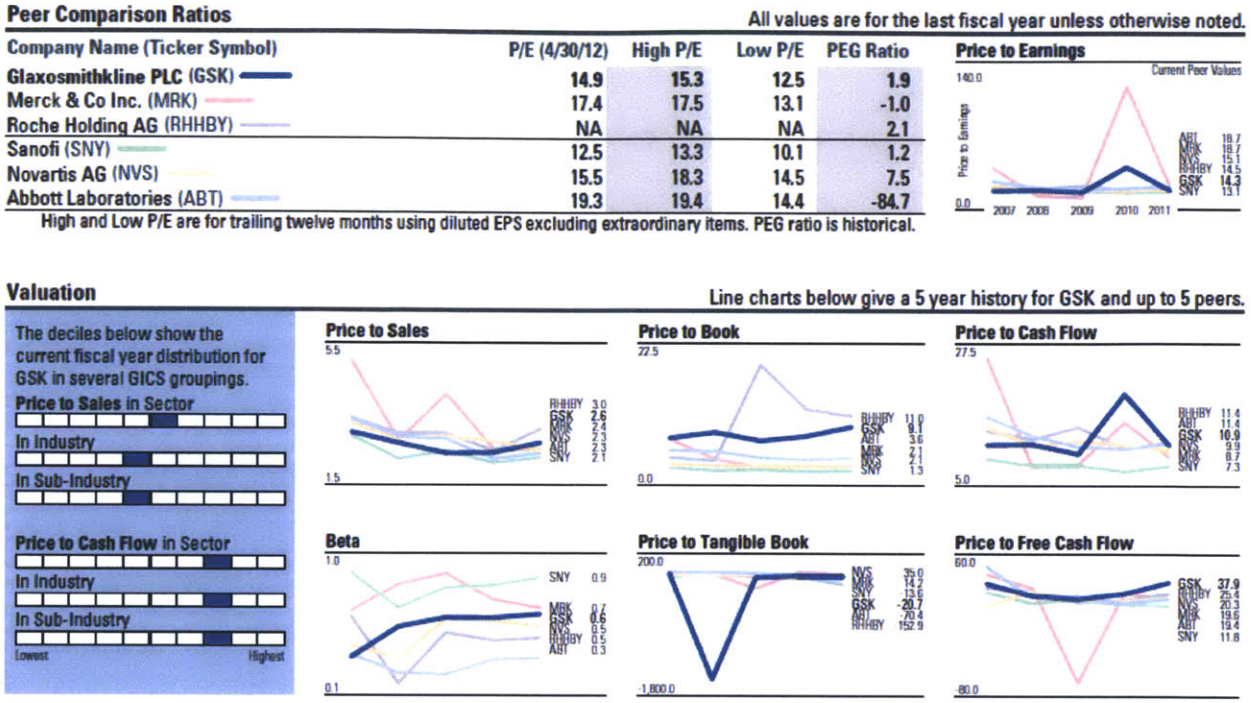


Fig. A.14. GlaxoSmithKline: company performance in comparison to its industry segment (2004 – 2012).

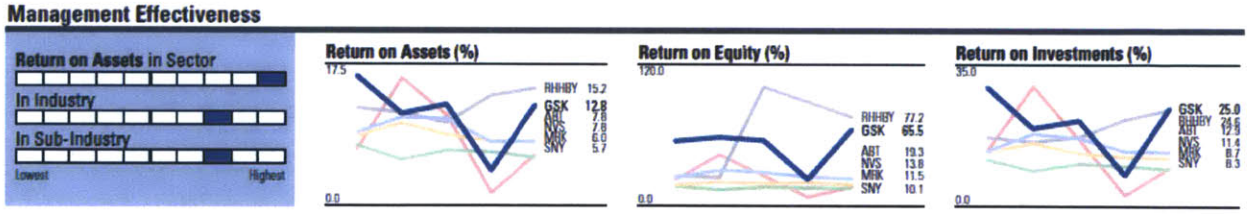


Fig. A.15. Management effectiveness of GlaxoSmithKline in comparison to selected peers in its

Selected Financial Data: Johnson & Johnson

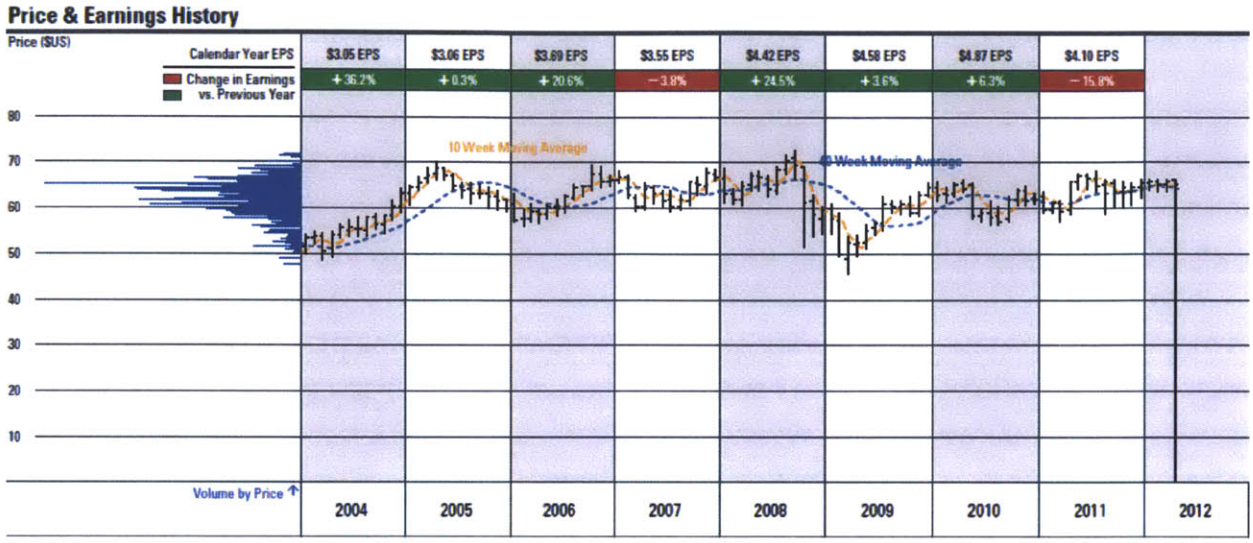


Fig. A.16. Johnson & Johnson (JNJ) price and earnings history as a function of its stock price (2004 – 2012).

Table A.6. Johnson & Johnson (JNJ) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	22.3x	17.4x	17.7x	18.4x	13.1x	14.6x	12.9x	18.8x	--
Price/Sales	4.0x	3.5x	3.6x	3.1x	2.6x	2.9x	2.7x	2.7x	--
Price/Book Value	5.9x	4.7x	4.9x	4.4x	3.9x	3.5x	3.0x	3.1x	--
Price/Cash Flow	17.7x	14.3x	14.4x	14.2x	10.5x	11.8x	10.4x	13.9x	--
Gross Margin	76.1%	76.5%	75.8%	75.5%	75.4%	74.9%	74.3%	73.7%	--
Profit Margin	18.0%	20.6%	20.8%	17.3%	20.3%	19.8%	21.7%	14.9%	--
Sales/Employee	$430.8 Th	$436.3 Th	$435.3 Th	$512.0 Th	$537.0 Th	$535.9 Th	$540.2 Th	$551.6 Th	--
Income/Employee	$77.4 Th	$90.1 Th	$90.5 Th	$88.7 Th	$109.1 Th	$106.2 Th	$117.0 Th	$82.0 Th	--
Return on Equity	26.7%	27.5%	28.1%	24.4%	30.5%	24.2%	23.6%	16.9%	--
Return on Assets	16.0%	17.9%	15.7%	13.1%	15.2%	13.0%	13.0%	8.5%	--
PEG (Historical Growth)	1.4x	1.0x	1.1x	2.2x	1.3x	2.6x	1.3x	-2.2x	--
Beta	0.2	0.3	0.3	0.1	0.5	0.6	0.6	0.6	--
Annual Dividend	$1.09	$1.28	$1.47	$1.64	$1.81	$1.93	$2.12	$2.26	--
Dividend Yield	1.7%	2.1%	2.2%	2.4%	3.0%	3.0%	3.4%	3.4%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

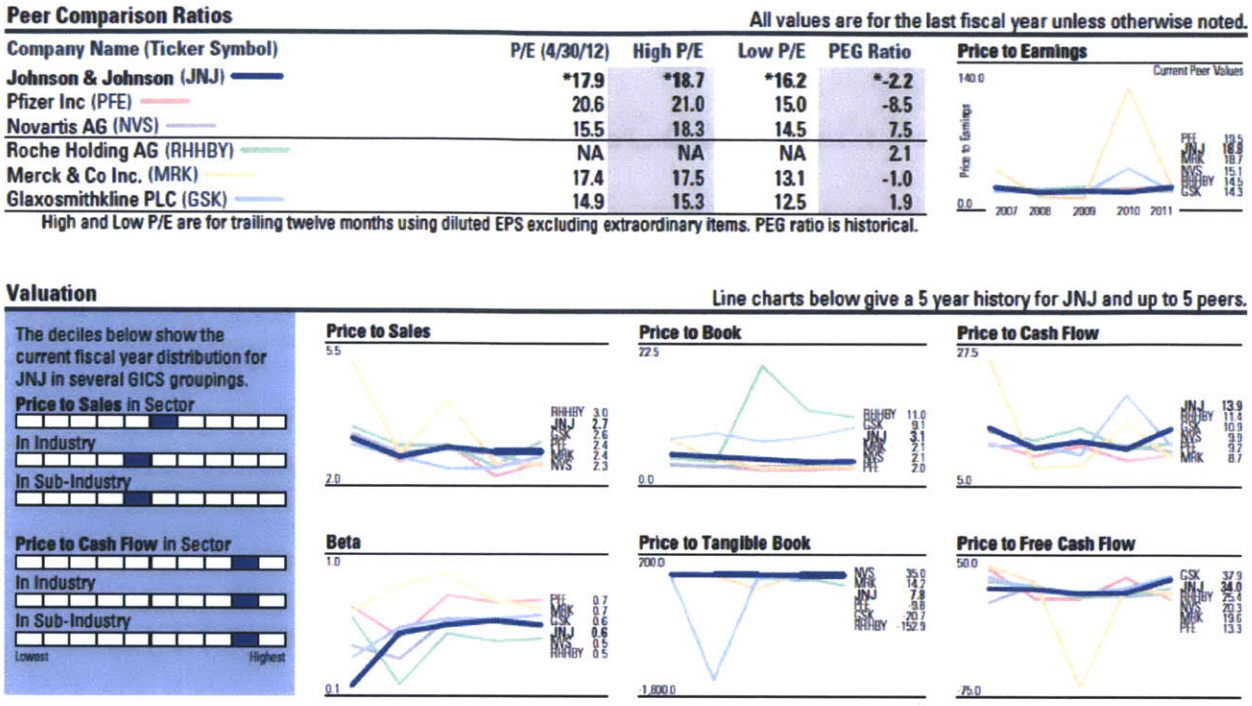


Fig. A. 17. Johnson & Johnson: company performance in comparison to its industry segment (2004 – 2012).

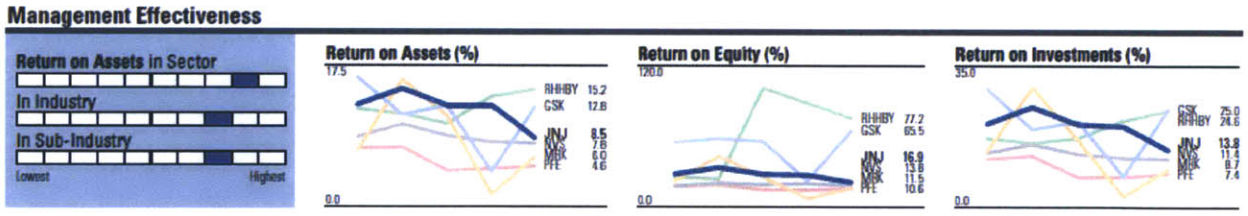


Fig. A. 18 Management effectiveness of Johnson & Johnson in comparison to selected peers in its industry segment.

Selected Financial Data: Merck & Company

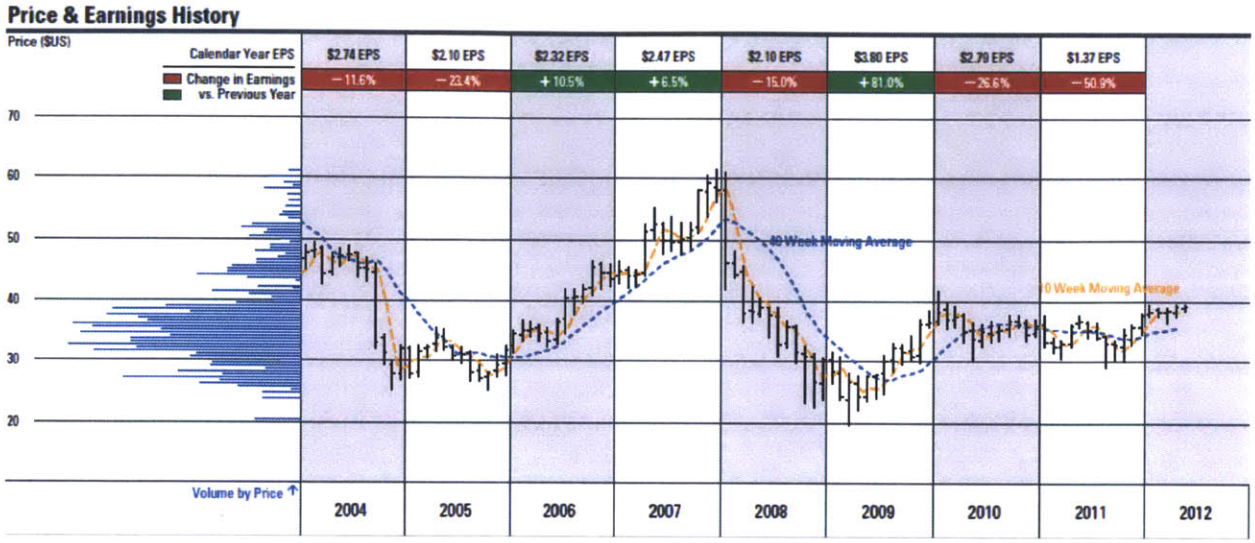


Fig. A.19. Merck & Company (MRK) price and earnings history as a function of its stock price (2004 – 2012).

Table A.7. Merck & Company (MRK) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	12.3x	15.1x	21.5x	39.0x	8.4x	6.5x	128.7x	18.7x	--
Price/Sales	3.0x	3.2x	4.2x	5.2x	2.7x	4.1x	2.4x	2.4x	--
Price/Book Value	4.1x	3.9x	5.4x	6.9x	3.4x	1.9x	2.0x	2.1x	--
Price/Cash Flow	9.8x	11.3x	15.9x	26.3x	6.9x	7.5x	15.0x	8.7x	--
Gross Margin	85.4%	84.9%	83.4%	82.9%	83.6%	82.0%	80.6%	80.6%	--
Profit Margin	24.8%	21.0%	19.6%	13.5%	32.7%	47.0%	1.9%	13.1%	--
Sales/Employee	$374.3 Th	$357.9 Th	$377.3 Th	$404.6 Th	$432.1 Th	$274.3 Th	$489.2 Th	$558.7 Th	--
Income/Employee	$92.9 Th	$75.3 Th	$73.9 Th	$54.8 Th	$141.5 Th	$129.0 Th	$9.2 Th	$72.9 Th	--
Return on Equity	33.6%	25.8%	25.2%	18.0%	41.6%	21.8%	1.6%	11.5%	--
Return on Assets	13.7%	10.3%	9.9%	6.8%	16.5%	11.5%	0.8%	6.0%	--
PEG (Historical Growth)	-2.1x	-1.2x	-1.9x	-2.3x	0.4x	0.2x	-3.0x	-1.0x	--
Beta	0.3	0.5	0.8	0.6	0.8	0.9	0.7	0.7	--
Annual Dividend	$1.51	$1.53	$1.53	$1.52	$1.54	$1.16	$1.53	$1.58	--
Dividend Yield	4.7%	4.8%	3.5%	2.6%	5.0%	4.2%	4.2%	4.1%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

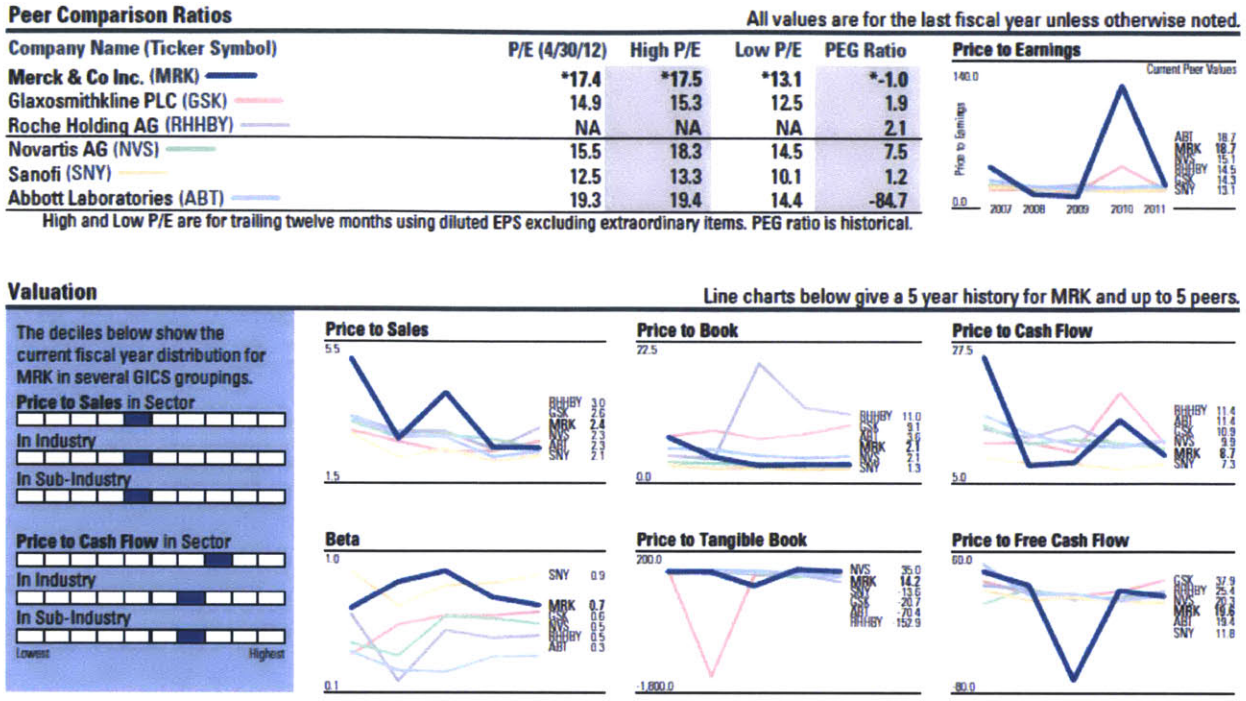


Fig. A.20. Merck & Company: company performance in comparison to its industry segment (2004 – 2012).

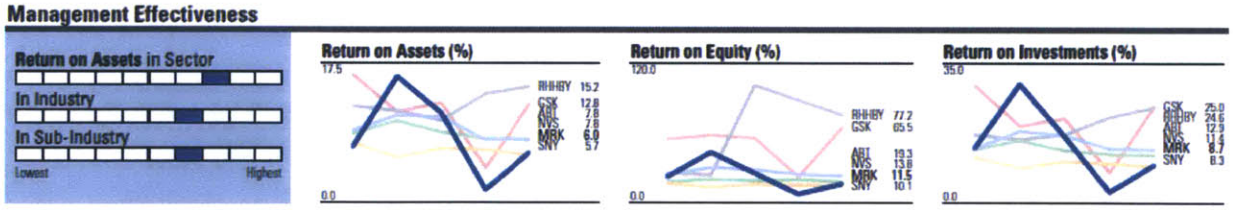


Fig. A.21. Management effectiveness of Merck & Company in comparison to selected peers in its industry segment.

Selected Financial Data: Novartis Pharmaceuticals

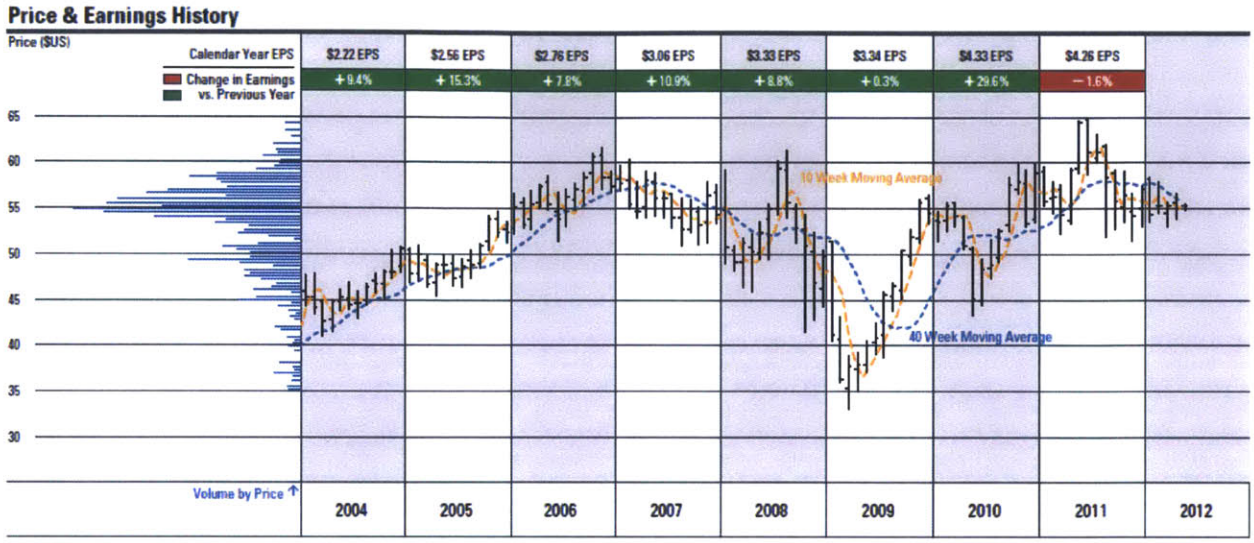


Fig. A.22. Novartis AG (NVS) price and earnings history as a function of its stock price (2004 – 2012).

Table A.8. Novartis AG (NVS) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	21.6x	20.0x	19.4x	19.4x	14.0x	14.8x	13.8x	15.1x	--
Price/Sales	4.3x	3.8x	3.7x	3.2x	2.7x	2.8x	2.7x	2.3x	--
Price/Book Value	3.6x	3.7x	3.3x	2.5x	2.2x	2.2x	2.1x	2.1x	--
Price/Cash Flow	17.6x	16.5x	15.3x	14.1x	10.8x	11.6x	11.0x	9.9x	--
Gross Margin	80.9%	76.5%	76.6%	77.7%	78.0%	77.6%	77.1%	76.0%	--
Profit Margin	20.4%	19.0%	19.4%	17.1%	19.6%	19.0%	19.3%	15.5%	--
Sales/Employee	$347.0 Th	$354.3 Th	$357.7 Th	$387.7 Th	$428.7 Th	$443.4 Th	$423.9 Th	$474.5 Th	--
Income/Employee	$70.9 Th	$67.4 Th	$69.4 Th	$66.4 Th	$84.0 Th	$84.1 Th	$82.0 Th	$73.7 Th	--
Return on Equity	17.1%	18.6%	16.9%	13.2%	16.2%	14.6%	15.5%	13.8%	--
Return on Assets	10.6%	10.6%	10.3%	8.6%	10.4%	8.8%	7.9%	7.8%	--
PEG (Historical Growth)	1.7x	2.4x	1.4x	3.1x	1.3x	1.9x	0.9x	7.5x	--
Beta	0.1	0.0	0.2	0.4	0.3	0.6	0.6	0.5	--
Annual Dividend	$0.81	$0.90	$0.87	$1.15	$1.48	$1.73	$1.96	$2.23	--
Dividend Yield	1.5%	1.7%	1.5%	2.0%	3.1%	3.1%	3.3%	4.1%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

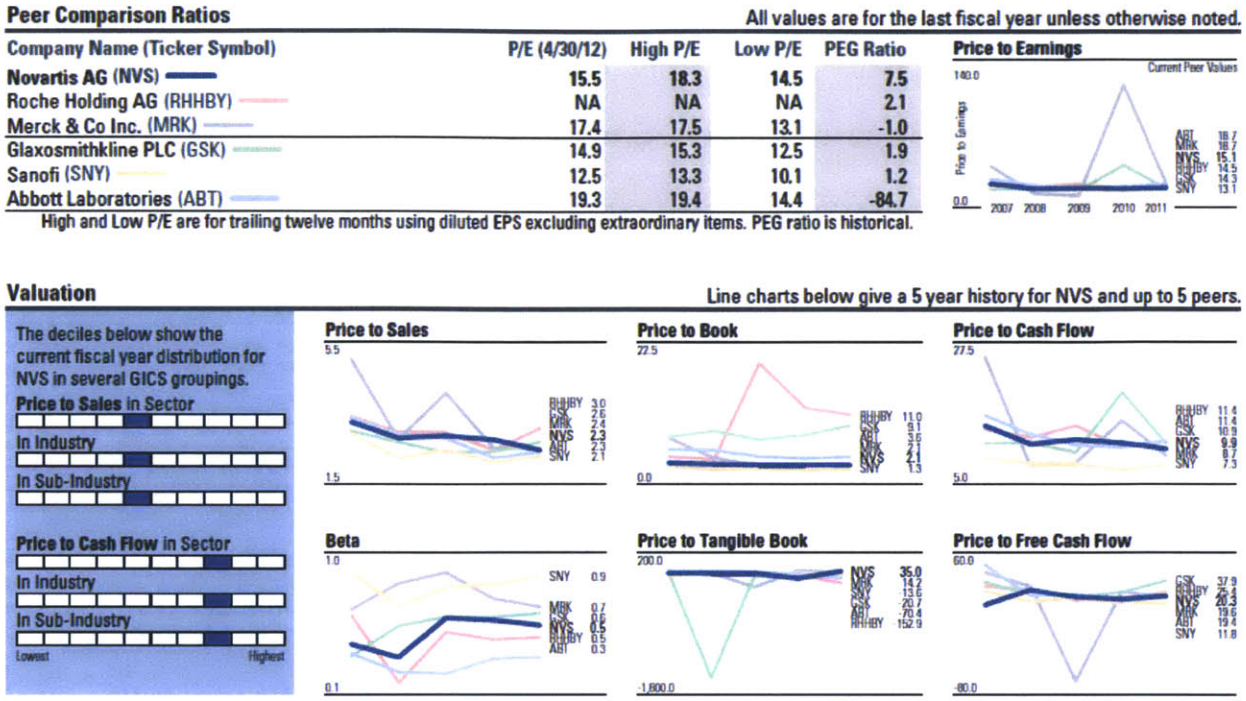


Fig. A.23. Novartis AG: company performance in comparison to its industry segment (2004 – 2012).

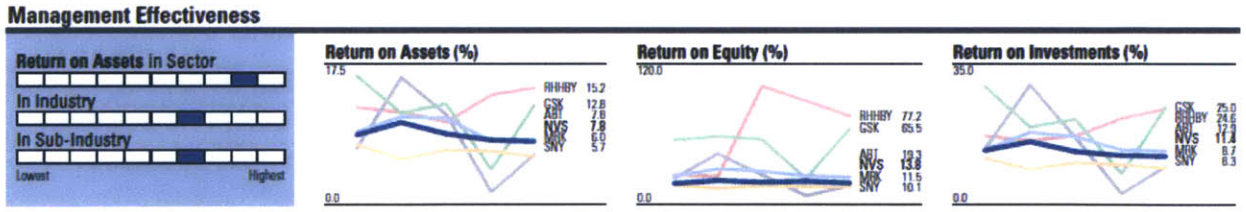


Fig.A.24. Management effectiveness of Novartis AG in comparison to selected peers in its industry segment.

Selected Financial Data: Pfizer Inc.

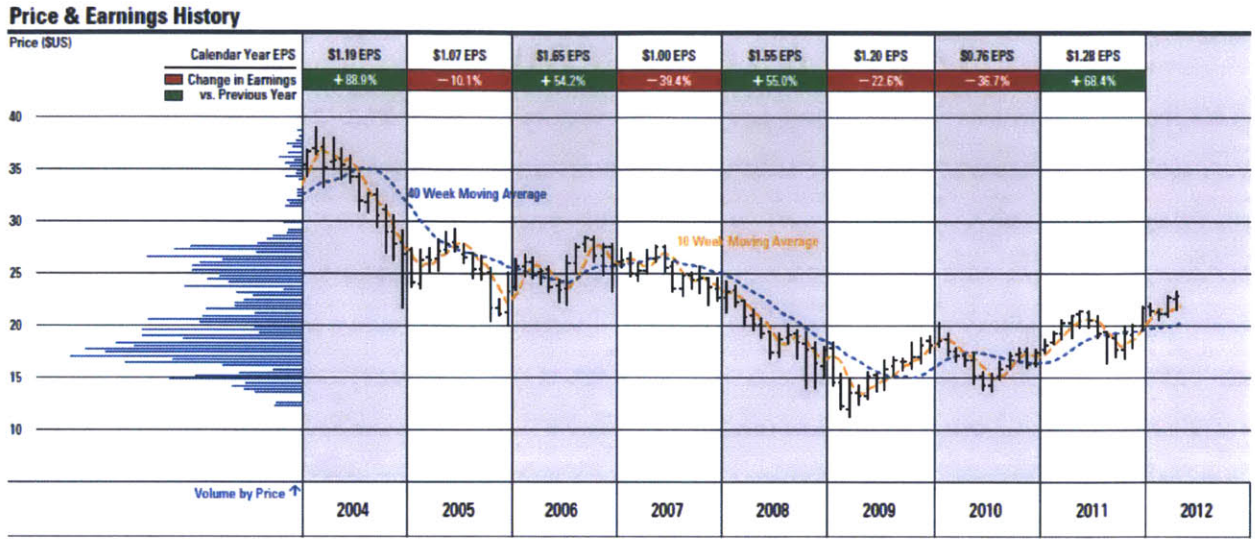


Fig. A.25. Pfizer's (PFE) price and earnings history as a function of its stock price (2004 – 2012).

Table A.9. Pfizer (PFE) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	18.0x	21.4x	17.0x	19.3x	14.9x	14.8x	17.2x	19.5x	--
Price/Sales	3.8x	3.3x	3.8x	3.2x	2.5x	2.9x	2.1x	2.4x	--
Price/Book Value	3.0x	2.6x	2.6x	2.4x	2.1x	1.6x	1.6x	2.0x	--
Price/Cash Flow	12.2x	12.6x	11.3x	11.5x	9.1x	11.0x	8.4x	9.2x	--
Gross Margin	88.9%	88.0%	89.2%	88.2%	90.1%	86.4%	81.6%	83.9%	--
Profit Margin	21.6%	15.8%	22.9%	17.0%	16.6%	17.3%	12.2%	12.9%	--
Sales/Employee	$456.7 Th	$483.9 Th	$491.8 Th	$556.7 Th	$591.0 Th	$428.6 Th	$612.9 Th	$650.2 Th	--
Income/Employee	$98.5 Th	$76.4 Th	$112.5 Th	$94.8 Th	$98.1 Th	$74.0 Th	$74.7 Th	$83.9 Th	--
Return on Equity	16.6%	12.4%	15.5%	12.6%	14.0%	9.6%	9.4%	10.6%	--
Return on Assets	9.2%	6.9%	9.6%	7.1%	7.2%	4.0%	4.2%	4.6%	--
PEG (Historical Growth)	2.6x	-2.3x	0.2x	-2.6x	5.0x	-2.2x	-3.6x	-8.5x	--
Beta	0.4	0.5	0.6	0.7	0.5	0.8	0.7	0.7	--
Annual Dividend	$0.70	$0.81	$1.02	$1.21	$1.28	$0.61	$0.74	$0.86	--
Dividend Yield	2.5%	3.3%	3.7%	5.1%	7.2%	4.4%	4.1%	3.7%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

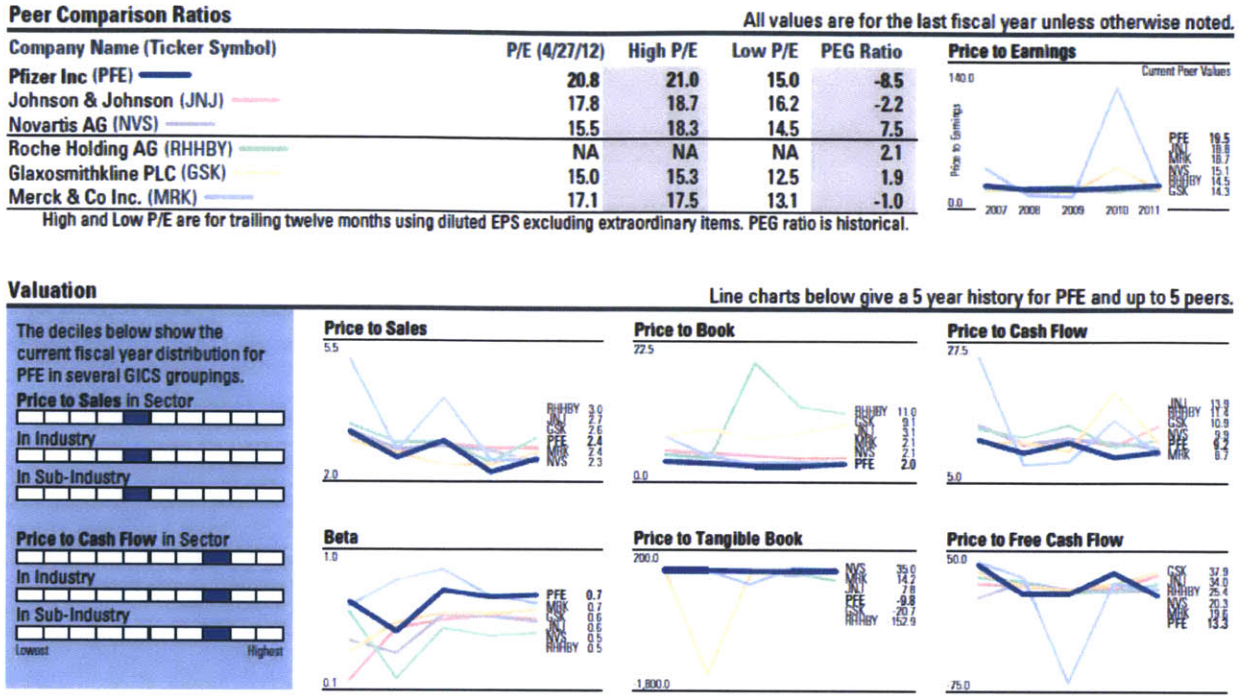


Fig. A.26 Pfizer (PFE): company performance in comparison to its industry segment (2004 – 2012).

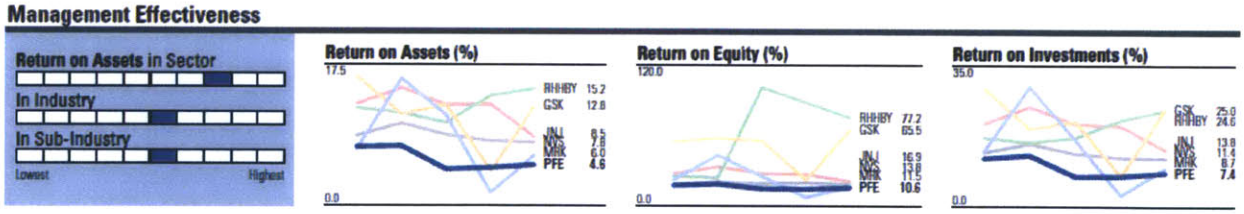


Fig. A.27. Management effectiveness of Pfizer in comparison to selected peers in its industry segment.

Selected Financial Data: Roche Holdings

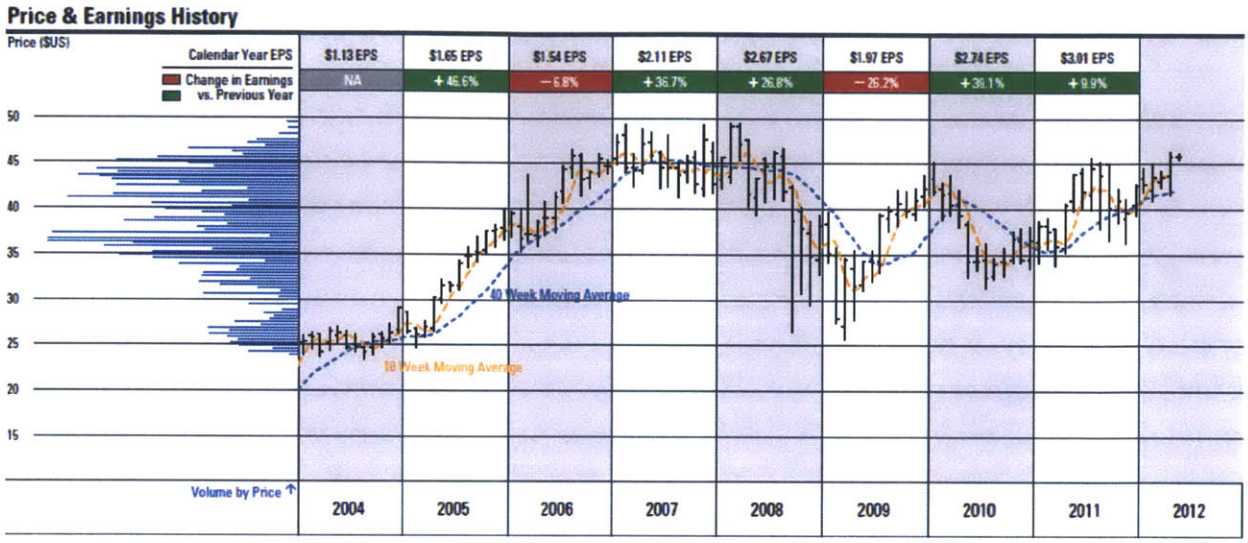


Fig. A.28. Roche Holdings (RHHBY) price and earnings history as a function of its stock price (2004 – 2012).

Table A.10. Roche Holdings (RHHBY) key financial data (2004 – 2012).

Fundamentals	2004	2005	2006	2007	2008	2009	2010	2011	2012
Price/Earnings	17.0x	29.3x	24.1x	17.3x	15.9x	19.4x	13.6x	14.5x	--
Price/Sales	3.4x	4.5x	4.3x	3.4x	2.9x	2.9x	2.4x	3.0x	--
Price/Book Value	3.9x	4.8x	3.9x	3.6x	3.1x	20.1x	12.2x	11.0x	--
Price/Cash Flow	12.5x	20.5x	18.0x	13.4x	12.0x	14.2x	10.3x	11.4x	--
Gross Margin	76.2%	78.5%	78.3%	76.8%	76.9%	76.7%	78.4%	78.9%	--
Profit Margin	20.1%	15.7%	18.2%	20.2%	18.7%	15.2%	17.6%	21.2%	--
Sales/Employee	$447.1 Th	$411.4 Th	$475.4 Th	$543.2 Th	$560.5 Th	$605.9 Th	$650.7 Th	$587.3 Th	--
Income/Employee	$89.9 Th	$64.7 Th	$86.7 Th	$109.6 Th	$104.9 Th	$92.2 Th	$114.7 Th	$124.4 Th	--
Return on Equity	23.5%	16.6%	16.8%	21.5%	20.2%	105.7%	91.5%	77.2%	--
Return on Assets	11.4%	8.4%	10.6%	12.5%	11.8%	10.4%	14.2%	15.2%	--
PEG (Historical Growth)	0.5x	2.1x	0.7x	1.3x	0.7x	3.5x	4.4x	2.1x	--
Beta	0.5	0.7	0.7	0.6	0.1	0.5	0.4	0.5	--
Annual Dividend	$0.37	$0.39	$0.52	$0.56	$1.09	$1.22	$1.63	$1.79	--
Dividend Yield	1.1%	1.1%	1.1%	1.6%	2.9%	2.5%	3.8%	4.2%	--

All values in the Fundamentals table are calculated using fiscal year data unless otherwise noted

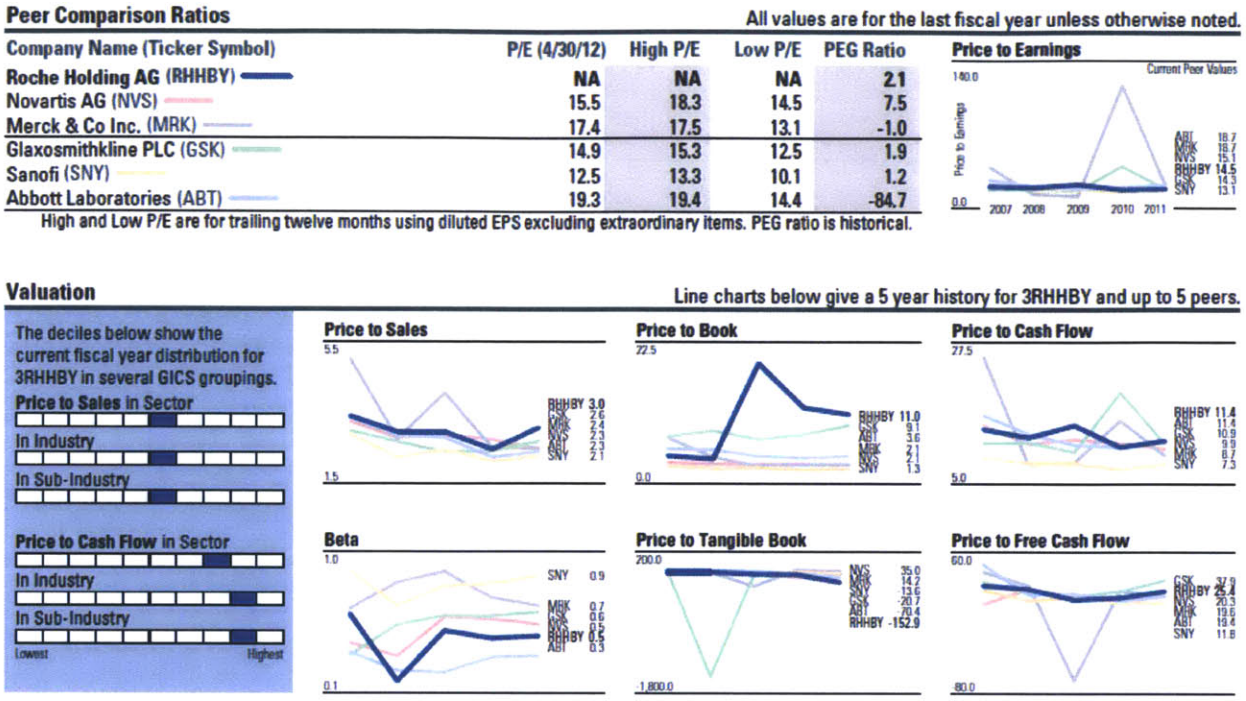


Fig. A.29. Roche Holdings (RHHBY): company performance in comparison to its industry segment (2004 – 2012).

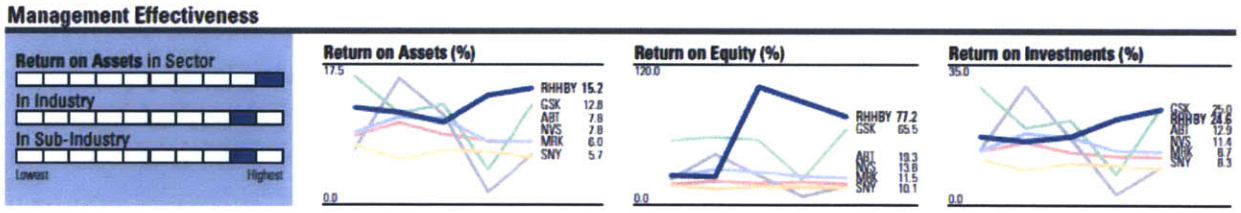


Fig. A.30. Management effectiveness of Roche in comparison to selected peers in its industry segment.

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