Chapter 1
Introduction

The pharmaceutical industry, a seemingly modern institution, actually had its origins thousands of years ago when primitive healers concocted potions derived from natural products to treat the illnesses and wounds of family members and fellow tribesmen. Over the centuries, virtually every society has recognized the special expertise of those individuals who could formulate medications by mixing together the proper ingredients in the correct dosages to achieve the desired therapeutic effects. From primitive healers to neighborhood pharmacists in more modern times—many of whom were affectionately known as "doc"—local healers have always regarded the patient's health as their top priority. Society, for its part, has always valued the ability to craft medicines to mitigate the discomfort of illnesses and cure diseases and has held those with these talents in high regard and rewarded them handsomely.

Advances in science and medicine during the twentieth century provided the foundation from which the pharmaceutical industry was able to grow rapidly over a relatively short period of time. In the past few decades, improvements in drug discovery chemistry and our understanding of the pathophysiology of disease at the molecular level have resulted in the development of unprecedented numbers of medications that reduce suffering and cure diseases (think antibiotics, cholesterol-lowering agents, and cancer drugs). The quest to discover and develop innovative new drugs to treat and cure disease is the financial engine that drives the pharmaceutical industry, a global business with forecasted sales of over $825 billion in 2010.[1] The United States is one of the largest and most profitable pharmaceutical markets ($300 billion in sales in 2009)[2] in the world and has been a global industry bellwether for the past fifty years; it will be the focus of this book.

Today, the search for new drugs is an extremely sophisticated process involving high-tech and arcane tools such as computer-assisted molecular modeling, nuclear magnetic resonance imaging

of protein structures, and an array of genomics- and proteomics-based screening assays.* Drug researchers also employ elaborately designed dosage formulations to optimize the pharmacokinetic profiles of drugs for precise dosing and delivery into the body so that they reach the appropriate site at effective but safe concentrations. Newer scientific and medical advances such as nanotechnology, stem cells, and gene therapy, while still in their infancy, add to the hope of cures for diseases previously considered untreatable death sentences. And while the availability of more and better products has led to the explosive growth of global pharmaceutical companies, the delivery of healthcare has also evolved and continues to do so in terms of how the market (e.g., government agencies, managed care organizations, hospitals, and private insurers) determines which medications to make available to patients at what cost. Unfortunately, the unintended consequences of pharmaceutical industry growth have compromised the traditional industry business model and put it in conflict with evolving market expectations. Eventually, the industry must fundamentally change how it does business to succeed in a more demanding environment where patients and healthcare providers have access to more information and payers and regulators play an increasingly larger role.

Despite the astounding technological advances that have occurred in medicine during the past fifty years, the need for disease-altering and curative treatments has not diminished. Human beings are now living longer than ever before; according to the National Center for Health Statistics, the life expectancy for males born in 2006 is estimated to be 75.1 years and for females 80.2 years.[3] Unfortunately, the aging process is accompanied by a host of illnesses and diseases (many of which are chronic and incurable) that underscore the continuing need for new therapeutic agents. Even if cures were found for the two hundred or so cancers that afflict humans, as well as Alzheimer's disease, diabetes, and many other debilitating conditions, millions of people would continue to hold out hope for therapeutic interventions that extend natural life expectancy through the use of pharmaceuticals,

* Genomics is the study of genes (segments of DNA that code for proteins) including their structure and function, while proteomics is the study of proteins (which are the actual "workhorses" in cells) including their molecular configuration and function.

vaccines, stem cells, nutriceuticals, or some other as yet to be discovered treatment option. And, at this point, the pharmaceutical industry (which includes biotechnology companies) represents the best hope for discovering and developing these new treatments into commercially available products for widespread use.

Unfortunately, drug development has not kept pace with the need for innovative new treatments; drug pipelines have dwindled recently, few truly innovative products are being introduced into clinical practice, and revenue growth in the pharmaceutical industry has slowed. At the same time, diminished public trust due to a host of missteps by the industry has led to intensified legislative and regulatory oversight and increased punitive litigation. This recent history is the backdrop for an industry that currently faces even more daunting challenges: looming patent expirations on billion-dollar blockbuster products, wholesale substitution of generic drugs for branded products, and intensifying pricing pressures. Add to these financial challenges the complexities of a fast-changing healthcare market and the uncertainties surrounding healthcare reform, and it is clear that pharmaceutical companies must change their business practices if they are to survive and prosper going forward.

A major premise of this book is that the rapid pace of advances in science and medicine combined with fast-changing healthcare market dynamics has created an increasingly complex environment for the pharmaceutical industry. The industry's complexity, along with its unbridled pursuit of revenue growth and profits to satisfy the expectations of "Wall Street" and secure personal financial gain for executives, has led to a series of missteps that are at the core of the industry's current state of dysfunction. Despite producing historically healthy profits and strong cash positions, doing business the same old way is no longer viable, nor will it be tolerated. The legislation just signed into law establishing healthcare reform in the U.S. will provide some near-term upside for the industry (approximately thirty million more Americans with prescription drug coverage), but capitalizing on these changes will be more difficult for companies that remain committed to the industry's traditional business model. If pharmaceutical companies do not change the way they do business, they will not be able to compete effectively in the evolving new healthcare market.

So how did the industry arrive at its current dysfunctional state? A little history is in order. Basking in the success of robust

product pipelines during the 1970s through the 1990s, the pharmaceutical industry took full advantage of an environment in which it could seemingly do no wrong. The healthcare market was inundated with thousands of sales representatives who peddled the "latest and greatest drugs" to physicians. A steady stream of new drugs including multi-billion-dollar blockbuster products, along with an intensified focus on commercialization (marketing and sales) and double-digit price increases drove revenues and profits ever higher. The pharmaceutical industry became a proverbial cash cow. Commercial success delivered an apparently endless cash flow that allowed companies to greatly increase their spending on research and development (R&D). Management, however, focused more on revenue generation, and, as a result, became less demanding of their R&D programs, settling for modest "quick to market" improvements in existing drugs rather than innovative new products.

Despite significant increases in R&D spending by pharmaceutical companies (which most would agree is a good thing), the push for innovation was undermined by an industry-wide dilution of expertise and the ease of chemically modifying existing compounds in the laboratory. These days, when promising new drugs are patented, other companies often rush to create similar but slightly modified "me too" drugs in order to capitalize on lucrative mass markets—such as hypertension[4] (high blood pressure) and hypercholesterolemia[5] (high cholesterol)—and extend their exclusive rights to the drugs they originally introduced.* While some of these "me too" drugs may have fewer side effects or improved dosing schedules (e.g., once or twice per day rather than three or four times per day), most provide little therapeutic advantage compared to the drugs that are already available to physicians and patients. Nevertheless, the ability to "pick off" even a very small share of a highly lucrative "chronic disease" market has the potential to generate substantial profits for companies.

* For example, there are now over 100 drugs on the market in the U.S. to treat hypertension. This should not be surprising given the fact that the market for anti-hypertensive drugs is projected to generate worldwide revenues of almost $30 billion per year by 2018. A similar situation exists with regard to the cholesterol-lowering drugs called statins, two of which (Lipitor® and Crestor®) generated over $16 billion in sales in the U.S. alone in 2008.

The pharmaceutical industry, with its established commercialization (sales and marketing) infrastructure and market dominance, has also been able to prolong the market exclusivity of its products by raising concerns about the quality and safety of generic drugs, thus temporarily fending off competition from these less expensive products. Despite having approved a wide range of generic drugs by the early 1990s, the Food and Drug Administration (FDA) was unable to convince patients and physicians that generic drugs were as safe and effective as branded drugs. The occasional adverse event (e.g., breakthrough seizures in patients taking generic anti-seizure medications) also reinforced physician and patient concerns regarding the quality, safety, and efficacy of generic drugs and delayed their acceptance, albeit temporarily.*

During this same period, biotechnology companies began to establish a foothold in the market with innovative protein-based (large molecules such as monoclonal antibodies) drugs for some of the more treatment-resistant diseases such as diabetes, stroke, arthritis, and cancer. These drugs were expensive to manufacture relative to traditional small molecules, but biotechnology companies were able to charge premium prices based on the uniqueness of the treatment, its superior clinical efficacy compared to what was available at the time, and, in the case of recombinant human insulin, its safety (e.g., far fewer allergic reactions) compared to traditional insulin, which is derived from the pancreases of cows and pigs.

In the midst of its successes in this challenging market, the pharmaceutical industry lost its philosophical grounding and put the financial expectations of Wall Street and personal financial gain ahead of the welfare of patients. As the cost of drug therapy increased to the point at which some patients had to decide literally whether to eat or buy their prescription medicines, the healthcare market (i.e., managed care, hospitals, insurance companies, consumers) began to fight back by instituting restrictive drug formularies, engaging in aggressive pricing negotiations through Pharmacy Benefits Managers, and developing a renewed interest

* Despite their widespread use, generic substitutions may be considered inappropriate for potentially toxic agents where the difference between an effective dose and a safe dose is small (e.g., the heart drug digoxin, anti-epileptic drugs, and the blood thinner Coumadin® all fall into this category).

in encouraging the use of cheaper generic drugs. In an attempt to appease Wall Street and investors who had become accustomed to annual growth rates of 10% or more, pharmaceutical companies responded by hiring more sales representatives and becoming much more aggressive in marketing their products. Some even resorted to increasingly desperate and at times illegal tactics including "off-label" promotion, fraudulent pricing schemes, and questionable payments and other inducements to healthcare professionals. Commercial success and "Big Pharma"* dominance in a challenging market also gave rise to a new level of industry-wide arrogance ("where else were people going to get their medicine?") that helped transform a previously supportive and grateful patient base into one that considered the industry and its high-priced drugs to be largely responsible for rising healthcare costs.

So how did this incredibly productive industry—one that employs so many highly educated people and that once enjoyed a stellar reputation—change so quickly and so dramatically? How did the industry's once robust new drug pipeline become relatively bereft of truly unique products? How could an industry that contributed so much to the health of a grateful nation come under intense scrutiny by Congress, the Justice Department, state legislatures, the private healthcare industry, the FDA, and consumers? After decades of advances, how did this once highly innovative, science-based industry become "commoditized" (many drugs, including generics, to treat the same symptoms and diseases) to the point where it now risks losing ground in the battle against such formidable diseases as cancer, diabetes, Alzheimer's disease, and life-threatening infections? It seems that decades of goodwill toward the industry for the development of treatments that reduce pain and suffering and often prolong life—from the commercialization of cortisone by Merck scientists in the 1940s to the development of highly sophisticated monoclonal antibodies such as Herceptin® (trastuzumab) that target cancer-inducing molecules today—have been squandered in a relatively few short years. What are the reasons behind the industry's rapid fall from grace? Is there a way to turn this around? Will industry research

* A somewhat pejorative nickname used to describe large pharmaceutical and biotechnology companies. In fact, the organization that represents the industry is aptly named the Pharmaceutical Research and Manufacturers of America (PhRMA).

deliver the promised innovative new products and cures that are still desperately needed? What changes do pharmaceutical companies need to make to compete effectively in the evolving new healthcare market? These are a few of the questions I will try to answer in this book.

The consequences of not resolving this situation may be catastrophic for the industry, the healthcare system, and for those patients who are in desperate need of new treatments or cures. While some critics believe that we can get along with the medicines already at our disposal, most would argue that we need a healthy pharmaceutical industry, as long as any new drugs they discover and bring to market are relatively inexpensive. Indeed, many people who enjoy a high standard of living and have easy access to healthcare may not see the critical need for a robust and healthy pharmaceutical industry, perhaps because healthy people often do not identify with those who are less healthy than they are. Indeed, this type of thinking may be one of the reasons we have continued to tolerate the lack of affordable healthcare for tens of millions of our citizens for so long. But, as demonstrated by the 2009 global H1N1 influenza pandemic, when large numbers of individuals become sick and an alarming number die, the availability of lifesaving medicine becomes increasingly important, and, in many cases, "the cost be damned." Yet few want to acknowledge or discuss the drug development challenges and substantial investments that are necessary to develop new medicines and bring them to market. Access to "experimental drugs," which may hold out the only hope for curing a disease or extending survival, becomes newsworthy only when prominent individuals become "patients." And yet, no one wants to hear the terrible news that "we have tried everything, and there is nothing more that we can do."

Many who believe that the industry is doing just fine and that it will eventually recover as it adjusts to the evolving healthcare paradigm are industry executives who have ignored the warning signs for years and continue to deny the troubled condition in which the industry now finds itself. As occurred with the near-collapse of the big financial institutions and the bankruptcy of the major auto companies, this state of prolonged denial has brought the pharmaceutical industry to the point where small incremental changes will have little sustainable effect on improving performance or mitigating the ill will fostered by decades of poor decisions.

Because of the large size of pharmaceutical companies, the magnitude and seriousness of past industry missteps, and the changes that a rapidly evolving healthcare market will bring, more dramatic interventions will be required to "right the ship."

So where do we start? In the next few chapters, I will provide some perspective on the challenges the industry has faced and identify the self-destructive behaviors that have led to the current state of dysfunction and illustrate why many of the industry's business practices need to be changed. Throughout the book, I will provide recommendations that, if implemented, can help transform pharmaceutical companies back to a favored position—one that enables them to function with integrity while carrying out the research and development programs that are vital to producing lifesaving treatments for those diseases that continue to exact a heavy toll on the human race. While these changes will be difficult and slow, the market has already demonstrated that it is more than willing to prescribe its own solutions for managing the industry and controlling the cost of drugs if pharmaceutical companies do not change the way they do business. For the industry, the implications of inaction are clear: prescription drug price controls, aggressive use of generic drugs, the requirement for proof of "comparative efficacy" superiority, and an end to influencing prescribers through traditional marketing and sales tactics. Against this backdrop, pharmaceutical companies will need a new business model to effectively participate and compete in this rapidly evolving healthcare market.