CHAPTER

1

Pharma's Reputation on A Slide

About a quarter of the money taken by pharmaceutical companies for the drugs they sell is turned around into promotional activity which has, as we will see , a provable impact on doctors' prescribing. So, we pay for products, with huge uplift in price to cover their marketing budgets, and that money is then spent on distorting evidence-based practice, which in turn makes our decisions unnecessarily expensive, and less effective.

—Ben Goldcare, Author of *Bad Pharma: How Drug Companies Mislead Doctors, and Harm Patients*

Pharma's Reputation on A Slide

Declining Reputation

Pharma's reputation has been going down these days. Pharma bashing, too, has become a popular game. The public perception of the pharmaceutical industry is currently at the lowest it has been in recent history. Consider, for example, the case of Merck, the company which was Fortune Magazine's most admired company in the US for an unprecedented seven years in a row. Paradoxically, it was the same Merck, the marketer of Vioxx, a product that experienced one of the most well-publicized drug recalls and ultimate withdrawal. Several books, such as *Bad Pharma* by Ben Goldacre, *The truth about the drug companies* by Marcia Angell, and *Hooked* by Howard Brody, described several areas of controversy, such as unethical marketing practices and lack of transparency. Magazines such as Forbes have devoted stories calling the industry 'Pill Pushers' and detailing how pharmaceutical companies have 'abandoned science for salesmanship.'

Good Practices

The behavior and practices of pharmaceutical companies determine whether their reputation is going north or south. In other words, what you do determines your reputation. Not very long ago, the pharmaceutical industry enjoyed a great reputation and even the admiration of all the stakeholders and the general public. They conquered many fatal diseases because of their significant contribution to society through their breakthrough discoveries in medicine. Here are some of the more important good practices that Pharma engages in :

- The industry plays a major role in discovering and developing new medicines.
- Responsible education of healthcare professionals (in particular physicians)
- The understanding of the true value of drugs for the appropriate patient populations. The recent advances towards

personalized healthcare by many specialty pharmaceutical companies indicate this.

- The Patients' quality of life improved with better diagnosis and compliance.
- The continuous use of clinical research supports the true value addition of drugs.
- Building up evidence concerning the needs and wants of patients to the R&D community and allocating more resources to the appropriate research projects.
- Planning and implementing patient-centric strategies from bench to bedside.
- Pharma companies have established R&D centers to work on cures for neglected diseases. Pharmaceutical companies are devoting resources to finding treatment for malaria, trypanosomiasis (sleeping sickness), dengue fever, and Chagas disease that plague the developing world. Many companies are working on these projects with the Gates Foundation, the United Nations Children's Fund (UNICEF), and World Health Organization (WHO).
- Companies such as GlaxoSmithKline have been running the African Malaria Partnership for a decade to implement behavioral change programs to aid malaria prevention in vulnerable areas.
- The industry has been known for its philanthropy too. In annual surveys of the most generous companies, pharmaceutical companies dominate the list.

Pharma's Bad Practices

Pharmaceutical companies have received their share of criticism in recent years, not only concerning their alleged profiteering but also for their behavior that led to excessive profits. The pharmaceutical industry's marketing practices have been particularly facing severe criticism. The areas which face criticism more often are:

- Excessive incentives for company sales reps
- Using their medical liaisons to promote products

- Excessive incentives to Key opinion leaders (KOLs) and physicians for prescribing the drugs
- Physician engagement practices. Campbell et al. in 2007 wrote in an article, *A national survey of physician-industry relationships* published in the New England Journal of Medicine, that out of 3,167 physicians surveyed, 94 percent of physicians had free food in their offices; 28 percent received consultancy fees for lectures or clinical trial recruiting; 35 percent received reimbursement for attending continuing medical education programs (CMEs) or professional meetings. This is only illustrative of the nature of physician engagement with Pharma.
- Off-label promotions
- Lack of transparency and deception over outcomes and scientific evidence for marketed products.
- The pharmaceutical industry spends more money on marketing than on research and development, and this marketing expenditure drives drug prices very high. In 2014, Global Data reported that Johnson & Johnson, Pfizer, and Novartis were spending almost double their R&D expenses on marketing while others, such as Roche and Lilly, almost equal amounts on marketing and R&D.
- Bribery: Transparency International in 2011 reported that the pharmaceutical industry ranked seventh out of 19 industries that use bribery to speed up administrative processes in 30 countries worldwide. GlaxoSmithKline's bribery charges in China, and Kickbacks to pharmacies in the US by Novartis are widely known.

These unethical marketing practices have been responsible for bringing the pharmaceutical industry's reputation down and not the marketing of prescription drugs per se. Lea Prevel Katsanis, a marketing professor, in her insightful book *Global Issues in Pharmaceutical Marketing*, suggested the following factors associated with reputational damage:

1. The pharmaceutical industry is an industry that is more inward-looking and resistant to change, with self-reinforcing beliefs about its marketing practices.

2. In-experienced marketing managers who manage brands and learn their skills on the job without sufficient formal training.
3. A lack of accuracy and balance in the presentation of marketing messages. The effects of this message multiply as it is repeated in multiple channels.
4. The use of direct-to-consumer advertising (DTCA) and how it trivializes drug therapy.
5. The belief is that if a particular marketing activity is legal, then by definition, it must also be appropriate. Pharmaceutical companies have a 'no apologies' approach regarding their marketing activities.
6. The perception of high drug prices is a consequence of sizable marketing budgets. The public, in particular, believes that pharmaceutical companies spend more on marketing than on research to develop new drugs, and this marketing activity results in higher prices.
7. The effects of physician engagement with the industry result in a potential bias toward prescribing the drugs.
8. The inaccurate medical news reporting and the blurred lines between legitimate news and marketing messages.
9. The perception is that the pharmaceutical industry sets its own agenda to determine disease treatment policies.
10. The public distrust of the industry results from the negative publicity given to off-label drug marketing.

Pharma's Bad Practices: Cases

Here are a few cases that illustrate some bad marketing practices by leading pharmaceutical companies providing the pharmaceutical marketer with valuable insights into what not to do and avoid.

CASE

1

The Vioxx Fiasco!

Merck discovered Vioxx (Rofecoxib), a Cox 2 selective inhibitor, by a team led by P. Prasit at Merck-Frosst in Montreal, Canada. Merck acquired Charles E. Frosst in 1965. FDA approved Vioxx in May 1999.

Vioxx was an anti-inflammatory drug used to treat arthritis and acute pain without stomach irritation caused by other non-steroidal anti-inflammatory (NSAID) drugs. Merck promoted Vioxx aggressively using direct marketing to doctors, private clinics, and hospitals through advertising campaigns both in print media and television. The drug was also endorsed by celebrities who were former athletes, such as Dorothy Hamill and Bruce Jenner. Merck also offered Vioxx to hospitals and doctors at discounted rates. As a result, Vioxx emerged as one of the best-selling drugs in treating arthritis and acute pain within one year of launch.

Termed Super Aspirin, Vioxx was promoted as a cure for everything from arthritis pain to menstrual cramps. In addition, it was projected as a pain reliever, which was a boon for patients suffering from arthritis. Moreover, Vioxx relieved pain without gastrointestinal problems caused by older-generation painkillers. Merck spent about $160.8 million promoting Vioxx in 1999. It soon emerged as one of the fastest-selling drugs in the world. Vioxx quickly became a

blockbuster drug for treating the pain associated with osteoarthritis (OA) and rheumatoid arthritis (RA).

However, even as the prescriptions and sales were increasing rapidly for Vioxx, so were the concerns about its side effects. Although Vioxx was considered gastro-safe as there were no gastrointestinal side effects, the same thing cannot be said about cardiovascular side effects. Medical experts have been raising doubts about the cardiovascular risks associated with Vioxx's long-term usage almost since its launch. In the initial years, Merck disagreed with the various medical studies that indicated cardiovascular risks until its own internal study indicated the risk.

Merck's VIGOR clinical studies published in 2004, showed a five-fold increase in myocardial infarction among patients taking Vioxx compared to patients taking Naproxen. In September 2004, clinical trials showed that Vioxx increased the risk of myocardial infarction and stroke. Immediately, Merck voluntarily withdrew Vioxx from the market on September 30.

The stock market reacted violently to Merck's withdrawal of Vioxx from the market, wiping out about $28 billion of the company's stock value in a few months.

Launched in May 1999, and withdrawn on September 30, 2004. During the short life of Vioxx, it had about 105 million prescriptions in the US. More than 84 million people had taken the drug worldwide, and at the time of recall, about 2 million were taking it. Soon after the recall, Merck's share prices fell by 27 percent from $45.07 to $33 per share, wiping out $28 billion in market value. Vioxx had been the fastest-moving drug in Merck's portfolio at the time of recall. What a fall! How did it happen? The timeline of events leading to the precipitous fall of Vioxx is presented in the following table.

Table 1.1 The Rise and Fall of Vioxx: A Timeline

Period	Actions and Activities
November 1998	Merck completes a clinical trial testing their Investigative New Drug (IND) on 5,400 subjects and seeks US FDA approval.
January 1999	Merck launches Vioxx Gastrointestinal Outcomes Research study (VIGOR) with more than 8,000 participants. Half of the participants take Vioxx and the other half take Naproxen, a pain killer and NSAID of an older generation. The clinical trial is designed to see whether Vioxx is safer for the gastrointestinal system than Naproxen.
May 1999	FDA approves Vioxx, making the drug available by prescription in the US.
October 1999	The VIGOR Study's Data and Safety Monitoring Board (DSMB) meets for the first time and notes that Vioxx patients have fewer ulcers and less gastrointestinal bleeding than patients taking Naproxen. It looks as if the study will be a success for Merck.
November 1999	The VIGOR Study's Data and Safety Monitoring Board (DSMB) meets again and focuses on heart problems. The panel finds that 79 patients out of 4,000 taking Vioxx have serious heart problems or have died, compared with 41 patients taking Naproxen. They note that while the trends are disconcerting, the number of events are small, and to continue the study.
December 1999	The safety panel observes that the risk of serious heart problems and death among Vioxx patients are twice as high as in the Naproxen group. The panel, while recommending the continuation of the study, decides that Merck needs to develop a plan to analyze the study's cardiovascular results before the study ends. When recommending the continuation of the study, the Safety panel said that it could not tell if Vioxx was causing the heart problems or if Naproxen, acting like a low-dose aspirin protected people from them, making Vioxx just look risky in comparison.
January 2000	Merck hesitates at developing the analysis plan. The company wants to wait and combine the cardiovascular results of VIGOR with the results from other Vioxx studies. But, Dr. Michael E. Weinblatt, the safety panel Chair and a rheumatologist from Brigham & Women's Hospital at Boston pushes for immediate analysis. Merck agrees to analyze heart problems reported reported by February 10 - at least a month before the last patient leaves the study. Events reported later won't be included in the initial analysis.

Table 1.1 *Contd...*

Period	Actions and Activities
February 2000	Dr. Michel E. Weinblatt files out a disclosure form that says he and his wife own $ 72,975 of Merck stock. He also agrees to a new contract involving 12 days of work over two years, at the rate of $ 5,000 per day.
March 2000	Merck gets the results of the VIGOR trial.
May 2000	Merck submits VIGOR study paper to the New England Journal of Medicine (NEJM) for publication. The data includes only 17 out of 20 heart attacks Vioxx patients had.
July - November 2000	A. A memo from Merck statistician Deborah Shapiro to Merck scientist Alise Reicin (both are listed authors of the NEJM paper) refers to heart attacks 18, 19, and 20 suffered by patients taking Vioxx during the study. B. Merck tells the FDA about the heart attacks 18, 19, and 20. C. VIGOR study authors submit two sets of corrections to their NEJM manuscript, without mentioning the three additional heart attacks D. NEJM publishes the VIGOR study results, still with no mention of the three additional heart attacks in the Vioxx group. The published results also leave out many other kinds of cardiovascular adverse events.
February 2001	The FDA holds advisory meeting on VIGOR trials. It publishes complete VIGOR data on its website, including the additional heart attacks and data on other cardiovascular events.
August, 2001	Cardiologists - Debabrata Mukherjee, Steven Wissen, and Eric Topol publish their meta-analysis in the Journal of American Medical Association (JAMA), based on complete VIGOR data that the FDA has made available.
January 2002 to August 2004	Numerous epidemiological studies point out that Vioxx increased risk of cardiovascular problems.
September 2004	A. Merck withdraws Vioxx after its colon-polyp prevention study -APPROVe shows that the drug raises the risk of heart attacks after 18 months. By the time Vioxx is withdrawn from the market, an estimated 20 million Americans have taken the drug. B. The decision resulted in a huge loss of $ 28 billion in market value for Merck. C. The number of lawsuits blaming Vioxx for the deaths of patients who were taking the drug also start mounting.

Table 1.1 *Contd...*

Period	Actions and Activities
July 2005	NEJM editor-in-chief, Dr. Jeffrey M. Drazen tells NPR that the journal had been hoodwinked by Merck and that the authors of the VIGOR study should have told the Journal about the additional heart attacks.
November / December 2005	A. NEJM issues an *Expression of Concern* writing that, inaccuracies and deletions in the VIGOR manuscript Merck submitted to the Journal call into question the *integrity of data*. The Journal asks the study authors to submit a correction to the Journal. B. The first Federal trial on Vioxx lawsuits begins in 2005 in New Jersey court.
March 2006	VIGOR study authors respond to NEJM's expression of concern stating: our evaluation leads us to conclude that our original article follows appropriate clinical trial principles and does not require a correction. The three additional heart attacks in question occurred after the study's respecified cutoff date for reporting cardiovascular problems.
May 2006	A. Outside analysis of data sent to the FDA from Vioxx APPROVe study show that the cardiovascular risks from Vioxx began shortly after patients started taking the drug. The data also indicated that the risks from Vioxx remain long after patients stop taking the drug. B. Merck disagrees with the analysis and maintains that patients are not at risk unless they had taken the drug for more than 18 months. This point is very important for Merck as it could cost the company billions of dollars. Many of those suing the company say that they took the drug for less than 18 months.
June 2006	A. The seventh trial against Merck begins. Out of six cases that have already gone to trial, Merck has won three and lost three. B. Research published in the medical journal, Lancet estimates that 88,000 Americans had heart attacks from taking Vioxx and 38,000 of them died.
November 2007	Merck announces that it will pay $4.85 billion to end thousands of lawsuits over its painkiller Vioxx. The amount paid into a settlement fund is believed to be the largest settlement ever.

Source: Snigdha Prakash, Vikki Valentine, The Rise and Fall of Vioxx: A Timeline, NPR, November 10, 2007

Vioxx's withdrawal had cost Merck dearly in loss of revenues, market capitalization, and reputation. What is paradoxical about the whole Vioxx fiasco is that Merck was banking on a gastro-safe drug and compared it with a drug, Naproxen, that is cardiac-safe but has serious gastrointestinal side effects like many NSAIDs. In the bargain, it has a gastro-safe drug with serious and fatal cardiovascular side effects. As Dr. Wayne Ray, an Epidemiologist at Vanderbilt University, aptly observed, "*A heart attack in exchange for an ulcer is a poor treatment.*"

(Source: Snigdha Prakash, Vikki Valentine, The Rise and Fall of Vioxx: A Timeline, NPR, November 10, 2007)

CASE

2

Marketing through Manipulation and Misinformation!

Parke-Davis, one of the leading American pharmaceutical firms, patented Gabapentin (Neurontin) in 1977, and obtained US FDA approval in 1993, as adjunctive therapy for partial-complex seizures. Neurontin became a significant blockbuster for Parke-Davis, which later became a division of Warner-Lambert by an acquisition. In 2000, Pfizer acquired Warner-Lambert.

Sales of Neurontin rose from US $95 million in 1995 to nearly $3 billion in 2004, after which its patent expired, and it lost most of its sales to the generics that flooded the market. How Neurontin became a three-billion dollar molecule is a story that is stranger than fiction and tells us that success at any cost is very costly! Here is a brief account of what happened:

The Early 1990s

Parke-Davis was facing serious challenges in the early 1990s. The patents of the company's blockbuster drugs had expired. The R&D pipeline, too, was nothing to write home about. Moreover, the stock market had downgraded the firm's stock. The company was in desperate need of something good to sell. The company hired a marketing consultant, Richard Vanderveer, with considerable knowledge of pharmaceutical marketing research and strategy. He helped the company institute a micro-marketing program.

Micro-marketing Program

Micro-marketing program is about targeting individual physicians with tailored information that resonates with them as individuals. The communication is target-specific or physician-specific, considering individual physicians' needs. It, therefore, would be highly interesting to doctors, unlike a carpet-bombing approach, where the same data and information are presented to all the physicians.

Around the same time, the company also hired Anthony Wild, who had considerable experience in the sales and marketing side of the pharmaceutical industry. He knew the task at hand when he joined Parke-Davis and was well aware of the crucial nature of his assignment. Moreover, he had a compelling need to succeed.

The 'Wild' Era

The company was banking all its hopes for future survival and growth on the two new drugs pending approval with the US FDA. One was Lipitor (Atorvastatin), a cholesterol-reducing drug; the other was Rezulin (Troglitazone) for treating type 2 diabetes.

Wild chalked out a survival plan for himself as well as the company. First, he identified three products among the existing product mix of Parke-Davis, which were not selling well, but had great potential. These products were - Neurontin (approved as an adjunct therapy in epilepsy), Accupril (Quinapril), an anti-hypertensive drug, and Loestrin, a low-estrogen birth control pill. He planned to raise the sales of each of these three brands to reach a 15 percent market share in their respective therapeutic categories. Moreover, he wanted to invest the profits generated by these three products in promoting the two new drugs once the company received approval from the FDA. He proposed his plan to the top management and got their approval.

Wild had set out to change the culture at the company. He focused on the following:

1. Change the somewhat fatalistic attitude at the company to a high-confident one. His message to the sales force? Believe in yourself!
2. From a risk-averse or low-risk stance to a high-risk, rich-rewards mindset
3. Removing all the caps or restrictions on sales force incentives and making them very attractive
4. Relentless focus on increasing the sales of Neurontin

Focus on Expanding Usage of Neurontin

Although the primary approval for Neurontin was in the adjunctive therapy of partial-complex seizures, the sales force was hearing favorable comments from doctors who had experimented with off-label uses of the drug to treat neuropathic pain, bipolar disorders, attention deficit disorders, migraine, restless legs syndrome, alcohol, and drug withdrawal and as a mono-therapy for seizures (instead of an adjuvant). Yet no reliable evidence proved Neurontin's benefits in treating these conditions. It was all anecdotal.

Conducting clinical trials for new drug applications was the only way to establish the efficacy of Neurontin in all these conditions. However, clinical trials were very expensive and were not guaranteed success. Moreover, Neurontin was coming off patent at four year-end; therefore, the huge investment in clinical trials would not be viable. Although charged with the new incentive system and all revved up, the sales force seemed helpless in expanding the sales. How could they increase sales without overtly promoting its off-label use, which was illegal? The company found its answer in the medical liaisons division. The primary responsibility of a medical liaison is to provide fair and balanced scientific information regarding clinical trials, drug uses, side effects, and adverse reactions and help physicians understand the state of the science and up-to-date information on

the treatment modalities. They should not engage in any way in persuading physicians to prescribe their products. The medical liaison executives are usually medical doctors or PhDs and should have the domain expertise comparable to physicians they visit to maintain a peer-to-peer status.

The company knew promoting its products and soliciting prescriptions through its medical liaison team was illegal, but it continued. But unfortunately, the company committed several unethical and even illegal actions in the process. Here is a very brief account of their so-called innovative marketing practices and what they did:

1. The company started hiring medical liaisons directly out of the sales department. They were all trained in sales techniques to generate prescriptions that the company needed very badly.
2. They also started incentivizing the medical liaisons by partly compensating them based on sales.
3. The medical liaisons had to work with the regular pharmaceutical representatives of the company and had no communication with the medical research division. The company gave their medical science liaisons a list of doctors for 'cold calls' based on the size of the doctors' practices and their potential to prescribe Neurontin. In addition, the company provided them with a package of monetary incentives to offer physicians for participating in the Parke-Davis programs.
4. Although it is illegal for a drug company to pay physicians to prescribe a drug, paying them to be special consultants is not technically illegal. Parke-Davis paid thousands of physicians to become such consultants. It is not a coincidence that all the physicians who received money from the company had one thing in common. They were all heavy prescribers of Neurontin, particularly for treating neuropathic pain.
5. At the time, Parke-Davis implemented a Preceptor program in which physicians who allowed a company representative to

visit included discussions with patients. As a part of the Preceptor program, representatives often had an opportunity to meet actual patients and influence the physicians often to prescribe Neurontin for off-label uses to treat these patients.

6. In addition, the company established a Parke-Davis speaker's bureau and paid high-prescribers of Neurontin *thought leaders* to go out and spread the word. However, there was no substantial clinical data. They only had data from their less rigorous case studies based on their clinical experience where they used Neurontin. The physicians were paid for these case studies on a case-by-case basis to write up each patient's history and response to Neurontin.

All these marketing practices led to a blatant off-label promotion of Neurontin. In April 1996, John Ford, the Parke-Davis Executive, articulated the company's expectations at a recorded marketing managers meeting. He said:

I want you out there every day selling Neurontin. Look, this isn't just me. It's come down from Morris Plains (Headquarters) that Neurontin is more profitable than Accupril. So we need to focus on Neurontin. Neurontin is not growing for adjunctive therapy (The approved indication). Besides, that's not where the money is. Pain management, now that's the money. Monotherapy, that's the money. We don't want to share these patients with everybody. We want them on Neurontin only. The whole thing is the drug budget, not a quarter or half. We can't wait for them to ask. We need to get out there and tell them out front. Dinner programs, CME (Continuing Medical Education) programs, and consultantships work great but don't forget the one-on-one. That's where we need to be, holding their hand and whispering in the ear, Neurontin for pain, Neurontin for mono-therapy, Neurontin for bipolar, Neurontin for everything. I don't want to see a patient coming off Neurontin before they've been unto 4,800 milligrams daily. I don't want to hear that safety crap either—you should take one just to see if there is nothing. It's a great drug.

The scale and magnitude of this change in Toni Wild's Parke-Davis were stunning and illegal. While the change apparently energized

the marketing team significantly, the legal downside too was substantial. As was mandatory, in April 1996, the company conducted a program to educate medical liaisons about the prevailing legal environment governing their role. A former FDA official and a company lawyer held a seminar on the subject. The seminar was in two parts; only the first part was videotaped. The FDA official and the lawyer said to the team:

If caught violating the FDA rules, you're on your own and acting without the company's knowledge or permission. You must have a physician information request (PIR) for each call. You must provide a fair and balanced presentation. You cannot close or sell. You can't promote a drug off-label. You cannot promote a drug pre-approval. You must keep an accurate record of your activities. You cannot solicit an inquiry.

After this, the video camera was turned off, and the second part of the seminar began. The second part of the presentation was candid and to the point. First, the former FDA official gave them tips on circumventing the system without getting caught. Then, it told the team what the company expected from them explicitly:

We expect you to do your job and stay focused on sales. Don't worry about this (the first part of the seminar). If you are cold calling a sales representative, have him fill out a physician information request form to cover you. The doctors know that you're not out there to help the competitors. So don't worry about being balanced in your presentation. Look, without sales, there is no Parke-Davis. We all have to sell at the same level. Be careful about this. Just don't leave anything behind. Above all, don't put anything in writing.

The medical liaisons soon became an integrated part of the sales and marketing department. The company gave them the same pep talk and offered the same incentives as it did for the sales teams. The company promised them an all-expense-paid cruise to the Bahamas if it achieved the sales goals for Neurontin and Accupril. A marketing executive told them:

The only way we will make it (to the Bahamas) is if you as a group take ownership of the task and get out there and aggressively move market share. You have to be aggressive. Don't take no for an answer. If the rep does not close, you close. If the rep sees the wrong doctors, you see the right ones. If a high-prescribing practice is not using Neurontin, get in there, do your thing, then ask why. I don't care, but you're wasting your time and our money if you don't ask for the new prescription when you are through.

Medical science liaisons soon dominated the Neurontin team. They were contacting more and more high-prescribing physicians as per the micro-marketing strategy. As a result, the physicians prescribed Neurontin for treating many off-label uses, such as bipolar disorder, neuropathic pain, and others. In addition, they focused on incentivizing these doctors and engaging them as part of the Neurontin family. As a result of all these activities, Neurontin achieved explosive growth reaching from a modest US $98 million in 1995 to a whopping US $3 billion in annual sales in 2004.

Finally, all the company's unethical and illegal promotional activities in promoting Neurontin had come to light because of a whistleblower, a new recruit in medical science liaisons. David Franklin, a post-doctoral fellow in microbiology from Harvard University, joined the medical sales liaisons at Parke-Davis on April 1, 1996. He attended the now infamous seminar that the former FDA official and the company lawyer gave the new trainees in medical science liaisons on April 16, 1996. A senior marketing executive repeatedly told Franklin to go out and sell Neurontin for off-label uses, contrary to the briefing he received at the training time. Franklin was disenchanted, disappointed, and confused by these conflicting messages. They were in total contradiction to what he perceived the medical science liaison job would be and the way it had turned out. He left Parke-Davis within three months, collected data and evidence about the firm's illegal marketing practices promoting Neurontin, and filed a suit against the company. Later, Pfizer acquired Warner and Lambert; thus, Parke-Davis became a part of Pfizer in 2000.

After protracted hearings and a detailed investigation into the allegations filed by Franklin, Pfizer pleaded guilty to its illegal

marketing practices and agreed to pay $430 million to resolve all the criminal and civil liabilities. The following table presents a timeline describing Neurontin's rise and the company's fall concerning its unethical marketing practices.

Table 1.2 Illegal Marketing of Neurontin: A Timeline

Period	Event
1977	Parke-Davis obtains a patent for its Gabapentin.
1993	US FDA approves Gabapentin under the brand name Neurontin as adjunctive therapy for partial-complex seizures.
1995	Neurontin records US $ 95 million in annual sales.
April 1, 1996	David Franklin, a post-doctoral fellow in microbiology from Harvard University joins Parke-Davis in Medical Science Liaison (MSL).
April 16, 1996	David Franklin and his peers get a briefing from Parke-Davis on FDA regulations and about their responsibilities as medical sceince liaison officers.
April 22, 1996	A senior marketing executive a week later repeatedly tells David Franklin to go and promote the drug Neurontin for off-label uses, which is contrary to the briefing Franklin had at the time of training.
August 1996	Franklin leaves Parke-Davis and files a suit against the company stating that it is indulging in illegal marketing practices such as off-label promotion of its drug Neurontin and making false claims to elicit payments from the Federal government. Case put under seal, deferring action pending government review.
December 1999	The government lifts the seal and litigation resumes.
2000	Pfizer acquires Warner Lambert along with its Parke-Davis division.
October 2000	The FDA approves Gabapentin (Neurontin) for adjunctive treatment of partial-seizures in children of 3 - 12 years.
May 2002	The FDA approves Gabapentin (Neurontin) for post-herpetic neuralgia in adults.
2004	Annual sales of Neurontin reach almost US $ 3 billion.
May 13, 2004	Warner-Lambert pleads guilty and agrees to pay US $ 430 million to resolve criminal charges and civil liabilities.

(Adapted from Greg Critser's book, Generation Rx: How Prescription Drugs Are Altering American Lives, Minds, and Bodies, Houghton Mifflin and Company, New York, 2005)

Predatory Pricing

Another bad marketing practice that pharmaceutical companies indulge is predatory pricing. Predatory pricing is the illegal activity of setting prices to eliminate competition and create a monopoly. Predatory pricing is also called undercutting. Usually, firms practicing predatory pricing strategies keep their prices low to make them unattractive to competitors. However, a new type of predatory pricing seems to be rearing its ugly head. It is predatory pricing in a reverse direction. Here the pricing strategy followed is to keep the prices very high, even to socially unacceptable levels, and yet keep competition at bay. When you can price your product so high, it must attract more competition, right? That is a logical question. But then, the modus operandi or the business model of these modern pharmaceutical predators on the prowl beats the logic. Their business model looks somewhat like this:

1. **Source a Sole-Source Drug**: Acquire a drug that had come off patent and yet remained a single source drug, which means that there is no imminent competition.
2. **Ensure that it is a Gold Standard**: Check that the single-source drug you acquired or are about to acquire is considered a gold standard for the condition it treats. If it is a gold-standard treatment, the physicians will continue to prescribe it even if the price increases. The perceived efficacy standard and the essential nature of the drug determine the level of price increase that it can absorb.
3. **Select a Drug that has a Smaller Market:** A smaller market means that it is relatively unattractive for competitors to enter. But ensure that the drug has smaller, dependent patient populations, who are too small to organize an opposition to price hikes.
4. **Closed Distribution**: Make sure when you acquire the drug meets all these criteria that it has a closed distribution system and is not easily available from any other sources. When the drug is unavailable through the normal channels, it creates another entry barrier for competition.

Once you acquire a drug meeting all the criteria mentioned above, the firm is ready to practice its predatory pricing strategy, which is in the reverse direction. While predatory pricing is pricing the product or service, keeping it so unattractively low that it becomes an entry barrier to competition. The new predatory pricing is to create entry barriers into their carefully chosen markets and then hike prices exorbitantly to maximize profitability.

CASE

3

Daraprim's Fifty-fold Price Increase!

Nobel Prize-winning American scientist Gertrude Elion developed Pyrimethamine (Brand Name: Daraprim) at Burroughs-Wellcome (GlaxoSmithKline, now) in 1952 to combat malaria. Pyrimethamine is on the World Health Organization's list of Essential Medicines because it is useful in treating parasitic infections such as Toxoplasmosis and Malaria and is often used for people with compromised immune systems, including AIDS and some forms of cancer, and elderly patients. Later in 2010, GlaxoSmithKline sold the marketing rights for Daraprim to CorePharma, which Impex laboratories later acquired in March 2015. Impex Laboratories sold the rights of Daraprim for the US market to Turing Pharmaceuticals in August 2015.

After purchasing Daraprim, Turing Pharmaceuticals increased the price of a single tablet almost fifty-fold from $13.50 to $750, raising the annual cost of treatment for some patients to hundreds of thousands of dollars. The price increase sparked widespread criticism. For example, the Infectious Diseases Society of America and the HIV Medicine Association sent a joint letter to Turing, stating the increase to be unjustifiable for the medically vulnerable patient population and unsustainable for the healthcare system.

In defense of Daraprim's price increase, the hedge-fund manager turned founder of Turing Pharmaceuticals, Martin Shkreli, said that

many patients use Daraprim for less than a year, and the price is more in line with other drugs for rare diseases. Moreover, Daraprim is 0.01 percent of healthcare costs in the US. Further, he promised to negotiate volume discounts for hospitals. He also claimed that a tablet would only cost $1for patients without insurance. Finally, he claimed: I'm like Robin Hood... I'm taking Walmart's money and researching diseases no one cares about, and the money from profits would be used to develop new and better drugs.

Several experts opined that price increase was unjustifiable on any count. For example, Dr. Wendy Armstrong, professor of infectious diseases at Emory University, said in response: *An old drug is not necessarily bad. Daraprim) happens to be an incredibly effective drug and has been cheap and well-tolerated by patients for years*.

Dr. Judith Alberg of Icahn School of Medicine at Mount Sinai said that *Daraprim would be too expensive for hospitals to keep in stock, and the use of the drug would require special review, possibly forcing the hospitals to seek alternative therapies that may not have the safe efficacy. Daraprim's price increase seems to be all profit-driven for somebody. I think it's a very dangerous process*.

Max Nisen wrote in Bloomberg and The Washington Post that: *Old medicines are sold at inflated prices because there's no mechanism to compel drug makers to lower them. So instead, pharmaceutical companies justify drug prices by reminding the public that developing drugs is costly and failure-prone. That's a fair point. But drug companies also announced more than $50 billion worth of share buybacks and dividend hikes after the new 2017 tax-cut law passed*.

In September 2017, Turing Pharmaceuticals became Vyera Pharmaceuticals and started marketing Daraprim in the US under the new company, Vyera Pharmaceuticals. The company responded to the 2015 criticisms of Daraprim with various patient affordability and access initiatives and reduced the cost of Daraprim to hospitals by up to 50 percent.

In January 2020, the FTC filed a case against Vyera alleging an elaborate anticompetitive scheme to preserve a monopoly for the life-saving drug Daraprim. In December 2021, Vyera Laboratories reached a settlement where the company agreed to provide up to $40 million in relief over ten years, to consumers who allegedly were fleeced by their actions and required to make Daraprim available to any potential generic competitor at the cost of producing the drug.

The Daraprim price increase did cause a lot of public outrage, and the CEO of Turing Pharmaceuticals, Martin Shkreli, was put behind bars for wire fraud. However, despite the outrage and legal action, prices for Daraprim have not decreased— one tablet still costs $750 at the time of writing in December 2022.

The concern here is that some predator marketers like Martin Shkreli scouring for drugs like Daraprim that don't have active generic rivals (as the market for such drugs is too small for a generic drug company to view it as profitable). So it is not a question of merely acquiring a drug and raising its price after acquiring the drug. Rather the issue is that these drug companies are strategically searching for drugs that can sustain massive price increases. It is a nefarious motivation, and there lies the moral fault.

(Source: Adapted from articles—(1) Ethics Unwrapped, Daraprim Price Hike, https://ethicsunwrapped.utexas.edu/video/daraprim-price-hike, (2) Ethics Unwrapped, Daraprim Price Hike, https://ethicsunwrapped.utexas.edu/video/daraprim-price-hike, (3) Wandtv.com, Prosecutors: Company that Illegally Monopolized Life-Saving Drug Must Pay $40 million, https://www.wandtv.com/news/prosecutors-company-that-illegally-monopolized-life-saving-drug-must-pay-40m/article_f16bea1a-5794-11ec-918c-af8ad2428046.html, and (4) Vyera Pharmaceuticals. (2022, August 13). In *Wikipedia*. https://en.wikipedia.org/wiki/Vyera_Pharmaceuticals, (5) Fritz Alhoff, *Daraprim and Predatory Pricing: Martin Shkreli's 5000% Hike* on Law and Biosciences Blog, Stanford Law Schools (SLS), Blogs, Stanford Law School)

CASE

4

Awareness Campaigns, Lobbying, Legislation, Competitors' Stumbles and Exorbitant Price Hikes Make A Blockbuster!

Can you believe that a company that did not know whether to keep a product that it acquired took it in-house, built a multi-pronged marketing strategy to market, and made it a blockbuster, a Go-to product for patients with severe allergies? The company is Mylan, and the product is their auto-injector device, EpiPen. Here is how it all happened.

Epinephrine (also known as adrenaline) that the body produces to increase blood flow to the muscles in its response to fight or flight. Jockichi Takamine, a Japanese chemist, was among the first to discover and isolate epinephrine. Soon after the discovery, scientists figured out how to produce it in large enough quantities and how to use it in different medical settings. In 1906, scientists synthesized epinephrine for the first time. Doctors continued investigating how adrenaline worked and have used it for over a hundred years. It has been studied extensively, with over 12,000 studies referencing it. It has heralded many areas of emergency medication. Epinephrine is used in hospitals worldwide and is on the World Health Organization's (WHO) essential medicines list. It only costs a few dollars a vial in the developed world and much less in the developing world.

In the 1970s, biochemical engineer Sheldon Kaplan invented a way to self-inject epinephrine called ComboPen. Initially, the US military used the ComboPen to protect their soldiers in the event of chemical

warfare, as it was easy to use in an emergency situation. Shortly after, Kaplan and others found out that they could use ComboPen to deliver epinephrine in emergencies to treat severe allergic reactions without the presence and help of healthcare providers. The US FDA approved the EpiPen as we knew it now in 1987. Meridian Medical Technologies, now a subsidiary of Pfizer, owned the product.

Later, Merck KGaA, a German drug company, acquired the product. Finally, in 2007, Mylan bought the generics business of Merck KGaA and became the owner of the EpiPen. Interestingly, Meridian continues to manufacture EpiPen for Mylan even today. In 2007, when Mylan acquired EpiPen, its annual sales were around US $200 million. In 2015, EpiPen's global sales passed the coveted one-billion-dollar mark. So how did Mylan achieve this? Here are some of the significant strategic steps that the company took:

1. Mylan specialty, the marketer and distributor of EpiPen auto-injector, launched many allergy and anaphylaxis awareness campaigns, both unbranded and branded, with celebrities living with or caring for someone with severe allergy conditions. The company ran, more recently, a *Face Your Risk* campaign, an ultra-realistic commercial about someone having an allergic reaction to peanut butter. Mylan spent a billion dollars to raise awareness of the need for EpiPens in the eight years from 2009 to 2016.
2. Mylan had also invested in a huge lobbying effort and got legislation passed in 48 states allowing schools to have undesignated EpiPens for emergency use.
3. Mylan has increased the price of a pack of two EpiPen auto-injectors exorbitantly from $93 in 2008 to $608.61 in 2016.

Mylan today has a virtual monopoly of the epinephrine market in the US, with over 90 percent market share. While these are the three main reasons for the phenomenal sales growth of Epipen, its price increase has been the most controversial and has drawn criticism from all corners of society. In response, the company increased its

copay coupon system and doubled the discount to $300 on a two-pack EpiPen auto-injector. In addition, the company announced sometime back that it would introduce a cheaper version of the EpiPen at half the current price.

The phenomenal sales success is due to many factors, such as awareness campaigns, lobbying leading to legislative changes, competitors' inability to field an approvable alternative, and an exorbitant price hike of 500 percent— some acceptable and some unacceptable.

Lessons

Mylan followed the classic marketing strategy behind every blockbuster drug meticulously. These are impactful disease awareness campaigns and lobbying to get the legislation to empower schools to provide EpiPen auto-injectors in time to treat medical emergencies due to severe allergic reactions.

Perhaps the most important lesson is that one should not exploit their monopoly situation and price it irresponsibly just to maximize profits at the expense of patients.

(Source: Adapted from articles— (1) Emily Willingham, Why Did Hike EpiPen Prices 400%? Because They Could, forbes.com, August 21, 2016, (2) Sarah Kliff, EpiPEn's 400 percent Price Hike Tells Us A Lot About What's Wrong With American Healthcare, vox.com, August 23, 2016)