Pfizer Pharmaceuticals: Green Chemistry Innovation and Business Strategy

Yujie Wang reviewed the presentation she had prepared for the executive committee's strategy meeting later that afternoon. Three of the committee members were familiar with the ideas and she could count on their support. Four others had pushed for new ideas to be fed into their group over the last year. Depending on the strength of her argument this time, they might be persuaded to support the project. The final two, who had significant responsibility for product development and operations, were somewhat less predictable. She had informed them of her progress during the project but they seemed disinterested at best. Then again, they were all busy people, and she had found it hard to schedule the intermediate briefings she wanted to bring everyone along. She knew the executives must be won over at least to a stance of "no opposition" to the proposal she would make.

Pharmaceuticals and Personal Care Products (PPCPs)

The objective of an efficacious pharmaceutical is to make certain molecules biologically active in humans. Not surprisingly, however, the same molecules that can cause desired results can have adverse effects in the body as well as post-patient—after the drug is expressed from the body and its active ingredients are released from disposal pipes into streams and other water bodies.

Regulations require extensive pre-testing of toxins in drugs (typically conducted by subcontractors) on different aquatic and mammalian species. Some critics argue the tests are sufficient; others question how accurately those surrogate studies can predict real results. Sweden, a nation that has aggressively studied chemical impacts on health and ecological systems, actively restricts non-benign drug manufacture and distribution, requires labeling of environmental toxins, and imposes sales caps and even bans. The European Union's 2005 Registration, Evaluation, Authorization, and Restriction of

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Chemicals (REACH) legislation would impose additional requirements on drug manufacturers (market size: 450 million).

According to the U.S. Environmental Protection Agency (EPA), PPCPs present scientific concerns for the following reasons:

> Large quantities of a wide spectrum of PPCPs (and their metabolites) can enter the environment following use by multitudes of individuals or domestic animals and subsequent discharge to (and incomplete removal by) sewage treatment systems. PPCP residues in treated sewage effluent (or in terrestrial runoff or directly discharged raw sewage) then enter the environment. All chemicals applied externally or ingested (and their bioactive transformation products) have the potential to be excreted or washed into sewage systems and from there discharged to the aquatic or terrestrial environments. Input to the environment is a function of the efficiency of human/animal absorption and metabolism and the efficiency of the waste treatment technologies employed—if any (sewage is sometimes discharged without treatment by storm overflow events, failure of systems, or "straight piping"). Removal efficiencies from treatment plants vary from chemical to chemical and between individual sewage treatment facilities (because of different technologies employed and because of operational fluctuations and "idiosyncrasies" of individual plants). Obviously, discharge of untreated sewage maximizes occurrence of PPCPs in the environment. No municipal sewage treatment plants are engineered for PPCP removal. The risks posed to aquatic organisms (by continual lifelong exposure) and to humans (by long-term consumption of minute quantities in drinking water) are essentially unknown. While the major concerns to date have been the promotion of pathogen resistance to antibiotics and disruption of endocrine systems by natural and synthetic sex steroids, many other PPCPs have unknown consequences. The latter are the focus of the ongoing U.S. EPA Office of Research and Development (ORD) work summarized here.[1]

Pfizer

In 2005, Pfizer employed 15,000 scientists and support staff in seven major labs around the world. Every weekday, 38,000 sales representatives sold Pfizer products. The company's $3 billion annual advertising budget made it the fourth-largest U.S. advertiser. In spring 2005, Pfizer was interviewing to fill the position of vice president of green chemistry. The new position reported to Dr. Kelvin Cooper, senior vice president, Worldwide Pharmaceutical Sciences, Pfizer Global R&D. The individual who would fill the position would need to examine the competitive challenges ahead, the internal progress to date, and ways to build on the successes of Zoloft and Viagra as examples of innovative green chemistry embedded in corporate strategy. In the short term, how

[1] U.S. Environmental Protection Agency (EPA). http://www.epa.gov/ppcp/ (accessed March 4, 2009).

could the company take the lessons learned from those two cases and apply them beneficially elsewhere?

Exploring those questions had been Yujie Wang's task for the past two months. The innovations provided dramatic cost savings, and the removal of toxic materials reduced both costs and risk. Given growing global attention to corporate accountability, increased government scrutiny of pharmaceutical companies, and the fast-growing popularity of sustainable business strategy, could adoption of a green chemistry strategy help Pfizer's reputation *and* offer opportunities for growth and profit? In this industry, companies competed primarily on drug offering and secondarily on process, with "maximum yield" as the main objective to maximize profitability.

Adding sustainability to the mix meant explicitly integrating human and community health, as well as ecological system preservation, into corporate performance. Sustainable development ideas introduced decades earlier had been transformed into business practices and were strategically implemented by well-known global companies such as Toyota, General Electric, Wal-Mart, Electrolux, and United Technologies. Wal-Mart and General Electric announced sustainability as part of their core strategy in 2005. The goal was to achieve financial success concurrently with these broader objectives.

Debate on climate change and discussion of pollutants' effect on human health and the environment had raised awareness of the human influence on natural systems; consequently, financial institutions and insurance companies were paying more attention to firms' existing and future liabilities. In the face of increased scrutiny by governments and nongovernmental organizations, firms were starting to assess their own vulnerabilities and opportunities with respect to such topics. "Sustainability" and "sustainable business" were two common terms in that discussion. Others in business used the phrase "triple bottom line," which referred to performance across financial, social, and ecological standards, or strategy attuned to economy, equity, and environment.

According to Joanna Negri, a process chemist and manager and a member of the company's green chemistry team, Pfizer "views sustainability and green chemistry as outcomes of good science—and this provides competitive business advantage through enhanced efficiency and safer processes."

Green Chemistry at Pfizer

In 2002, Pfizer won the U.S. Presidential Green Chemistry Award for Alternative Synthetic Pathways for its innovative manufacturing process for sertraline hydrochloride (HCl). Sertraline ("sir-tra-leen") HCl was the active ingredient in the pharmaceutical Zoloft. Zoloft—in 2005, the most prescribed agent of its kind—was used to treat clinical depression, which struck more than 20 million American adults and cost society nearly

$44 billion annually. As of February 2000, more than 115 million Zoloft prescriptions had been written in the United States; 2003 global sales grew to $3.11 billion.[2]

Applying the principles of green chemistry, Pfizer dramatically improved the commercial manufacturing process of sertraline. After meticulously investigating each of the chemical steps, Pfizer implemented green chemistry technology for this complex commercial process, which required extremely pure product. As a result, Pfizer significantly improved both worker and environmental safety. The new commercial process (referred to as the "combined" process) offered dramatic pollution prevention benefits, including improved safety and material handling, reduced energy and water use, and double overall product yield.[3] That success inspired green chemistry enthusiasts at Pfizer to look for other manufacturing processes to which the principles could be applied.

Complicating matters, however, was the state of the pharmaceutical industry in 2005; it was beleaguered by multiple issues affecting brand and profit margins, criticism of industry's policies on access to drugs in poorer communities, and lawsuits resulting from unexpected side effects. Could greener processes provide Pfizer an edge in this shifting landscape? Would it generate both the cost savings needed to justify the effort and the social capital that would support Pfizer's reputation, brand, and even its license to operate?

In 2001, informal conversations at a conference at the University of Massachusetts's Center for Sustainable Production marked the beginning of Pfizer's involvement in green chemistry. While there, Dr. Berkeley Cue, then vice president of pharmaceutical sciences research at Groton Labs (reporting to Pfizer Global R&D's Cooper) was surprised to learn that some Pfizer environment and safety chemists in attendance shared his interest. Impressed by the green chemistry work of professor and chemist John Warner at the University of Massachusetts, Cue believed the approach held potential for Pfizer.

From 2001 to 2004, Cue built a group at Groton, pulling in the discovery chemists from R&D to optimize products from the design stage. In talking with other R&D sites at Pfizer, the network quickly spread to the U.K. offices and Pfizer's R&D center in La Jolla, California. When Pfizer purchased Pharmacia in 2003, the company discovered that some of their new acquisition's R&D people were interested in green chemistry. Cue described his role as supporting a bottom-up initiative: "I brought people together in a tactical way and provided resources to give them a strategy and a voice upwards in the organization, and out."

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[2] PharmExec.com. http://pharmexec.findpharma.com/pharmexec/data/articlestandard//pharmexec/202004/95192/article.pdf (accessed March 4, 2009).

[3] U.S. Environmental Protection Agency (EPA). http://www.epa.gov/greenchemistry/pubs/pgcc/winners/gspa02.html (accessed March 4, 2009).

In late 2003, a steering committee formed to address the importance of the ideas for the corporation overall. Soon the active proprietary ingredients (API) chemists joined in and communication about the ideas expanded into legal and corporate affairs and R&D/manufacturing co-development teams. The committee communicated the message up and down the corporate hierarchy. Even the global marketing division was interested in the potential of this approach. By 2005, Pfizer had green chemistry activity in all seven of its R&D sites and had even begun to educate the federal oversight agency for the pharmaceutical industry, the Food and Drug Administration (FDA). (The FDA, with its legislative commitment to not compromise patient safety, was a demanding taskmaster that could dictate significant green chemistry changes to production that, although beneficial, would require long approval time frames.)

E-Factors and Atom Economy

Green chemistry is the design of chemical products or processes that eliminates or reduces the use and generation of hazardous substances. The application of green chemistry principles provided a roadmap that enabled designers to use more benign and efficient methods.

The industry used an assessment tool called E-Factor to evaluate all major products. E-Factor was defined in this industry as the ratio of total kilograms of all materials (raw materials, solvents, and processing chemicals) used per kilogram of active product ingredient (API) produced. Firms were identifying drivers of high E-Factor values and taking actions to improve efficiency.

A pivotal 1994 study indicated that for every kilogram of API produced, between 25 and 100 kilograms or more of waste was generated as standard practice in the pharmaceutical industry, a figure that was still common to the industry in 2005. Multiplying the E-Factor by the estimate of kilograms of API produced by the industry overall suggested that for the year 2003 as much as 500 million to 2.5 billion kilograms of waste could be the byproduct of pharmaceutical API manufacture. That waste represented a double penalty: costs associated with purchasing chemicals that are diverted from API yield; and costs associated with disposing of that waste (ranging from $1 to $5 per kilogram). Very little information was released by industry competitors, but a published 2004 GlaxoSmithKline life-cycle assessment of their API manufacturing processes revealed that 75 to 80 percent of the waste produced was solvent (liquid) and 20 to 25 percent solid, of which a considerable proportion was likely hazardous under state and federal law.

For years pharma said it did not produce significant enough product volumes to be concerned about toxicity and waste, particularly relative to commodity chemical producers, but with the competitive circumstances changing, companies were eager to find ways to cut costs, eliminate risk, and improve their image. After implementing its award-winning process in sertraline manufacture, Pfizer’s experience suggested green chemistry–guided process changes brought E-Factor ratios down to 10 to 20 kilograms. The potential to dramatically reduce E-Factors through “benign by design” principles

could, indeed, be significant. Lilly, Roche, and Bristol Meyers Squibb—all winners of Presidential Green Chemistry Awards between 1999 and 2004—reported improvements of this magnitude after applying green chemistry principles.

Predictably, green chemistry also fit with "Six Sigma," a methodology that considers waste a process defect. "Right the first time" was an industry initiative backed by the FDA. Groton's Cue viewed green chemistry as a lens that allowed the company to look at processes and yield objectives in a more comprehensive way, with quality programs dovetailing easily with this approach.

Pfizer Company Background

Charles Pfizer and his cousin, Charles Erhart, created Pfizer Inc. in 1849 in Brooklyn, New York. The company, today the world's largest drug company, began its climb to the top of the industry in 1941, when it was asked to mass-produce penicillin for the war effort. In the 1950s, the company opened branches in Belgium, Canada, Cuba, Mexico, and the United Kingdom and began manufacturing in Asia, Europe, and South America. Pfizer expanded its research and development, introducing a range of drugs and acquiring consumer products such as BenGay and Desitin, and by the mid-1960s, Pfizer's annual worldwide sales had grown to $200 million.[4]

Pfizer engaged in the discovery, development, manufacturing, and marketing of prescription medicines, as well as over-the-counter products, for humans and animals. In 2003, 88 percent of Pfizer's revenue was generated from the human pharmaceuticals market, 6.5 percent from consumer health care products, and 4 percent from animal health products.[5] Pfizer was traded on the New York Stock Exchange as ticker PFE. Its major competitors included Merck & Co. of Germany and Johnson & Johnson, GlaxoSmithKline Plc, and Novartis—all in the United States.[6]

Throughout the world, more than one billion prescriptions were written for Pfizer products in 2003.[7] In 2004, 14 of their drugs were top sellers in their therapeutic categories, including Zoloft, erectile dysfunction therapy Viagra, pain management Celebrex®, and cholesterol-lowering Lipitor®.[8] Its many over-the-counter remedies include Benadryl® and Sudafed®. Subsidiaries in the Pfizer pharmaceutical group included Warner-Lambert, Parke-Davis, and Goedecke. In 2000, Pfizer merged with Warner-Lambert, moving the company into the group of top five drug makers in the world. Pfizer then acquired pharmaceuticals company Pharmacia in 2003, making it the largest drug company in the world. This acquisition allowed Pfizer to diversify its product

[4] Dow Jones Reuters Business Interactive LLC (trading as Factiva). Pfizer Inc.. 2003.

[5] Pfizer Inc., 8K Filing and 2003 Performance Report, Exhibit 99. January 22, 2004.

[6] Business and Company Resource Center. Pharmaceuticals Industry Snapshot. 2002.

[7] Pfizer Inc., 8K Filing and 2003 Performance Report.

[8] Business and Company Resource Center.

line, because Pharmacia owned a range of therapeutic products in new areas, such as oncology, endocrinology, and ophthalmology.[9] The merger, which cost Pfizer $54 billion, also greatly expanded its pipeline through Pharmacia's research in atherosclerosis, diabetes, osteoporosis, breast cancer, neuropathic pain, epilepsy, anxiety disorders, and Parkinson's disease. By 2004, Pfizer had locations in 80 countries and sold products in 150 countries. In 2003, Pfizer also began selling some of its non-pharmaceutical businesses, such as the Adams confectionary unit (to Cadbury Schweppes) and Schick-Wilkinson Sword shaving products (to Energizer Holdings).[10] Pfizer was headquartered in New York and, in 2005, had four subsidiaries involved in pharmaceuticals, consumer health care and animal health care. Three subsidiaries conducted their business under the Pfizer company name, the fourth as Agouron Pharmaceuticals.

Pfizer posted total revenues for 2003 at $45.2 billion worldwide, an increase of 40 percent from 2002, and net income of $3.9 billion. While the company's largest market was in the United States, Pfizer's international market grew 56 percent in 2003, to revenues of $18 billion. Japan was its second-largest single national market.[11] "[Pfizer's] portfolio of leading medicines, which spanned most major therapeutic categories, drove Pfizer's strong revenue growth in the fourth quarter and full-year 2003," according to Karen Katen, executive vice president of the company and president of Pfizer Global Pharmaceuticals. In fall 2004, Pfizer appeared well positioned for continued industry leadership. Pfizer projected strong financial performance. The company had a target of $54 billion for its 2004 revenue and planned to spend about $7.9 billion in R&D during 2004.[12] "In the dynamic environment of today's worldwide pharmaceutical industry," said David Shedlarz, executive vice president and chief financial officer, "Pfizer is uniquely well-positioned to sustain our strong and balanced performance, leverage past and future opportunities, reinforce and extend our differentiation from others in the industry, and exploit both our operational flexibility and our proven abilities to execute."[13]

Industry Challenges

Despite Pfizer's optimism and past financial success, by early 2005, the entire pharmaceuticals industry suffered from a devastating lack of customer trust. From 1990 to 2004, the industry experienced a series of well-publicized criticisms. Most contentious amongst these critiques was the accessibility of AIDS drugs to patients in southern Africa. Analysts such as Merrill Goozner, former chief economics correspondent for the *Chicago Tribune*, suggested in 1999 that private pharmaceutical companies contributed to the global AIDS crisis by claiming that lowering the price of drugs or easing patent

[9] Business and Company Resource Center.

[10] *Ibid.*

[11] *Pharmaceutical Business Review* [online].

[12] Pfizer Inc., 8K Filing and 2003 Performance Report.

[13] *Ibid.*

protection for manufacturers in third-world countries would "stifle innovation."[14] In 2004, products from a flu vaccine production plant in the United Kingdom, critical to the U.S. supply, were blocked due to health and safety concerns. The same year, New York Attorney General Elliot Spitzer filed suit against pharmaceutical giant GlaxoSmithKline, saying that the company concealed important information about the safety and efficacy of Paxil®, an antidepressant drug. Adding to the controversy surrounding the pharmaceutical industry, popular filmmaker Michael Moore announced plans in 2005 to create a documentary called *Sicko,* which would use interviews with physicians, patients, and members of Congress to expose an industry that Moore claimed "benefits the few at the expense of the many."[15]

A poll conducted in December 2004 showed that Americans held pharmaceutical companies at the same low esteem as tobacco companies.[16] The pressure on Pfizer grew in late 2004 when prescriptions for its Celebrex pain relief and arthritis drug fell 56 percent in December following the company's announcement that the drug was linked to cardiovascular risk (heart attacks and strokes), a problem similar to Merck & Co.'s billion-dollar blockbuster drug Vioxx® (Merck, which was suspected of concealing Vioxx's potentially lethal side effects to maintain sales, withdrew it from the market in September 2004, undermining both public confidence in the pharmaceutical industry and the regulatory oversight of the FDA.[17]); Pfizer ceased advertising Celebrex. In December 2004, the S&P 500 Pharmaceutical Subindustry Index was down 12.8 percent for the year, though the S&P 500 was up 6.8 percent.

The pharmaceutical industry was a high-risk, high-reward business. Consumers demanded lifesaving drug discoveries that were safe and affordable. In the United States, drug patents only lasted for five to 10 years, so pharmaceutical companies were constantly threatened by generic competition. In 2004, it cost an estimated $897 million to develop and test a new medicine; about 95 percent of chemical formulas failed during this process. In 2002, the FDA approved only 17 new drugs, the lowest number since 1983. In an attempt to boost innovation, pharmaceutical R&D skyrocketed, with Pfizer investing $7 billion on R&D in 2003, leading the industry by a margin of several billion.[18]

In 2005, Pfizer managed the world's largest private pharmaceutical research effort, with more than 13,000 scientists worldwide. That tremendous investment, however, was not translating into drug output, which had been spiraling downward since 1996. In January 2005, Pfizer had 130 new molecules in its pipeline of new medicines, along with 95

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[14] Goozner, M. Third World Battles for AIDS Drugs. *Chicago Tribune*. April 28, 1999.

[15] Dutka, E. Giving Them a Sick Feeling. *Los Angeles Times.* December 22, 2004. http://articles.latimes.com/2004/dec/22/entertainment/et-sicko22

[16] Angell, M. Big Pharma is a Two-faced Friend. *Financial Times.* July 19, 2004.

[17] Agovino, T. Drug Industry Weathers Horrid Year and Outlook Appears Rocky.. Associated Press. December 16, 2004.

[18] Rotman, D. Can Pfizer Deliver? *Technology News.* February 2004.

projects to expand the use of current therapies.[19] To meet its 2005 revenue goal of double-digit growth, Pfizer planned to file applications for 20 new drugs before 2010.[20] Analysts viewed that unprecedented growth rate skeptically, saying that Pfizer had only seven drugs in the FDA testing phases.

From 1993 to 2003, Pfizer spent about $2 billion on drugs that failed in advanced human testing or were pulled off the market due to problems such as liver toxicity. Thus, Pfizer decided in 2005 to shift R&D focus to analyzing past failed drug experiments to find patterns that might help detect toxicity earlier in the expensive testing process.

From 1995 to 2005, pharmaceutical companies invested significant R&D funding into genomics experiments, which were very expensive and yielded less-than-revolutionary results. After a decade of investments in high-powered genomic tools, pharmaceutical companies were in their most prolonged and painful dry spell in years. “Genomics is not the savior of the industry. The renaissance is in chemistry,” said Rod MacKenzie, Pfizer’s vice president of discovery research in Ann Arbor, Michigan.

Brand Protection

To counteract a growing reputation that Pfizer was unwilling to engage with certain NGOs, Pfizer was one of the earliest of the few U.S. companies to sign the voluntary U.N. Global Compact defining principles for corporate behavior, including human rights, labor, and the environment. The U.N. Global Compact was designed to open dialogue between business, governments, NGOs, and society-at-large. The compact requires use of the precautionary principle, a guide to company decision-making that assumed, “lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.”[21] A study in 2003 by the International Institute for Management Development in Geneva found that stakeholders expect more social responsibility from the pharmaceutical sector than from any other industry. Pfizer transformed its quarterly “Financial Report” into a “Performance Report,” which included updates on corporate citizenship;[22] the *Chronicle of Philanthropy* rated the company “the world’s most generous company.”

In the pharmaceuticals industry, innovation can be stifled by the complexity of global business, science, government, religion, and public response, all colliding over issues of life and death. AIDS was driving high demand for more breakthrough medicines but at an affordable price. “We have learned that no single entity—whether business,

[19] Nielson, N. Pfizer, A New Mission in Action. *Learning to Talk: Corporate Citizenship and the Development of the UN Global Compact*. Greenleaf Publishing: Sheffield, UK, 2004.

[20] *Ibid.*

[21] United Nations Rio Declaration on the Environment and Development, 1992.

[22] Nielson, N. Pfizer, A New Mission in Action. *Learning to Talk: Corporate Citizenship and the Development of the UN Global Compact*. Greenleaf Publishing: Sheffield, UK, 2004.

government, or NGO—can alone bridge the deep divides between poverty and affluence, health and disease, growth and stagnation. As the world's foremost pharmaceutical company, we have an important obligation to take a global leadership role," Pfizer Chairman Hank McKinnell commented.[23]

In 2000, Pfizer conducted focus groups at several Pfizer locations around the world to create a new mission. First, it was decided that Pfizer would measure itself on a combination of financial and non-financial measures, reflecting stakeholders' changing expectations of business. Second, Pfizer would no longer measure itself solely against others in the pharmaceuticals industry, but against all other companies in all industries. The new mission statement is:

> We will become the world's most valued company to patients, customers, colleagues, investors, business partners, and the communities where we live. This is our shared promise to ourselves and to the people we serve. Pfizer's purpose is to dedicate ourselves to humanity's quest for longer, healthier, happier lives through innovation in pharmaceutical, consumer, and animal health products.

Pfizer stated that it measured progress as putting people and communities first; operating ethically; being sensitive to the needs of its colleagues; and preserving and protecting the environment.

In 2002, Pfizer donated $447 million to programs like its Diflucan Partnership Program, which provides healthcare training and free medicine to treat HIV/AIDS-related infections to patients in Africa, Haiti, and Cambodia. That year, Pfizer also held an internal symposium on green chemistry, a design approach that continued to drive manufacturing toward more benign material use.

In 2003, Pfizer became a member of the World Business Council on Sustainable Development, the International Business Leaders Forum, and Business for Social Responsibility—organizations that provide resources to firms to promote sustainable business practices internationally, sometimes referred to as the triple-bottom-line performance (economy, environment, equity). Pfizer set a company goal for 2007 to reduce carbon dioxide emissions by 35 percent per million dollars of sales and, by 2010, supply 35 percent of global energy needs through cleaner sources. Pfizer is a member of the U.S. Environmental Protection Agency's Climate Leaders Program, a voluntary industry-government partnership. Pfizer was again included in the Dow Jones Sustainability Asset Management Index, a global index that tracks the performance of leading companies, not only in economic terms but also against environmental and social standards.

[23] Medicines to Change the World. Pfizer's 2003 Annual Review. http://www.pfizer.nl/pdf/annualreportpfizer2003.pdf (accessed March 4, 2009).

Zoloft

Zoloft was released in 1992 and was approved for six mood and anxiety disorders, including depression, panic disorder, obsessive-compulsive disorder (OCD) in adults and children, post-traumatic stress disorder (PTSD), premenstrual dysphoric disorder (PMDD), and social anxiety disorder (SAD).[24] Zoloft was the most prescribed depression medication, with more than 115 million prescriptions written in the United States in its first seven years on the market.[25] According to Pfizer's 2003 filings, Zoloft brought in $3.1 million in worldwide revenue, with $2.5 million coming from the U.S. market. Those revenues show an increase of 16 percent worldwide—14 percent in the United States and 23 percent internationally during the fourth quarter of 2003, compared to the same period of the previous year.[26] Zoloft sales comprised approximately 9 percent of Pfizer's total U.S. sales in 2003, second only in sales percentage to Lipitor.

In 2002, Pfizer was awarded the Green Chemistry Award for Alternative Synthetic Pathways. Pfizer received the award for its development of the sertraline process, an innovative process for deriving Zoloft, in which sertraline is the active ingredient. Since developing the new process in 1998, Pfizer successfully implemented it as the standard in sertraline manufacture. To make Zoloft, a pure output of sertraline must be isolated from a reaction that occurs in solvent (or in a combination of solvents). The "combined" process of isolating sertraline was the third redesign of the commercial chemical process since its invention in 1985.[27] Each of those redesigned reactions decreased the number of solvents used, thus simplifying both the process (through energy required and worker-safety precautions) and the resulting waste disposal. The traditional process used titanium tetrachloride, a liquid compound that was toxic, corrosive, and air-sensitive (it formed hydrochloric acid when it came in contact with air).[28] It was used in one phase of the process to eliminate water, which reversed the desired reaction if it remained in the mix. In the process of "dehydrating" this step of the reaction, the titanium tetrachloride reacted to produce heat, hydrochloric acid, titanium oxychloride, and titanium dioxide. Those byproducts were carefully recovered and disposed, which required an additional process (energy), inputs (washes and neutralizers), and costs (waste disposal). The new process blended the two starting materials in the benign

[24] Medicines to Change the World. Pfizer's 2003 Annual Review. http://www.pfizer.nl/pdf/annualreportpfizer2003.pdf (accessed March 4, 2009).

[25] U.S. Environmental Protection Agency (EPA), Green Chemistry Challenge, 2002 Alternative Synthetic Pathways Award. http://www.epa.gov/greenchemistry/pubs/pgcc/winners/gspa02.html (accessed March 4, 2009).

[26] Pfizer Inc., 8K Filing and 2003 Performance Report, Exhibit 99. January 22, 2004.

[27] EPA Green Chemistry Application, Pfizer, Green Chemistry in the Redesign of the Sertraline Process. 2002.

[28] *Ibid.*

solvent ethanol and relied on the regular solubility properties of the product to control the reaction. By completely eliminating the use of titanium tetrachloride, the “combined” process removed the hazards to workers and the environment associated with transport, handling, and disposal of titanium wastes.[29] Using ethanol as the solvent also significantly reduced the quantities of one of the starting materials, and allowed for this material to be recycled back into the process, increasing efficiency.

Another accomplishment of the new process was discovering a more selective catalyst. The original catalyst caused a reaction that created unwanted byproducts. Removing these impurities required a large volume of solvent as well as substantial energy. Also, portions of the desired end-product were lost during the purification process, decreasing overall yield. The new, more selective catalyst produced lower levels of impurities, which, in turn, had the effect of requiring less of the reactant (mandelic acid) for the next and final reaction in the process. Finally, the new catalyst was recovered and recycled, providing additional efficiency.

By redesigning the chemical process to be more efficient and produce less harmful or expensive waste products, the “combined” process of producing sertraline provided both economic and environmental/health benefits. Typically, 20 percent of the wholesale price was manufacturing costs, of which approximately 20 percent was the cost of the tablet or capsule, with the remaining percentage representing all other materials, energy, water, and processing costs. With generics on the horizon, achieving materials and processing cost reductions could prove a decisive capability differentiator.

Subsequent to receipt of the green chemistry award, Pfizer realized an even more efficient process driven off the earlier successes. The starting material for sertraline, called tetralone, contained an equal mixture of two components: one produces sertaline; the other forms a byproduct that must be removed, resulting in a process that is only half as productive. Using a cutting-edge separation technology called multiple-column chromatography (MCC), Pfizer scientists were able to fractionate the starting material into the pure component that results in sertraline. The other component can be recycled back to the original 1:1 mixture, which could be now mixed with virgin starting material and resubjected to MCC separation. This new process was reviewed and approved for use by the FDA. The net result was twice as much sertraline produced from a unit of starting material, and half the manufacturing plant capacity was required per unit of sertraline produced.

A Depressing Decree from the United Kingdom

In December 2003, the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom included Zoloft (sold in the United Kingdom as Lustral®) on a list of antidepressants banned from use for the treatment of children and teenagers

[29] EPA Green Chemistry Application, Pfizer, Green Chemistry in the Redesign of the Sertraline Process. 2002.

younger than age 18.[30] The safety and efficacy of the drugs was in question, a query brought to the attention of U.K. health officials after high rates of suicide were observed in patients taking certain antidepressants. Of the major antidepressants, only Eli Lily's Prozac is currently permitted for use in U.K. children.[31] Pfizer immediately put out a statement disagreeing with the findings of the MHRA, claiming that their "controlled clinical-trial data in pediatric and adolescent depression shows no statistically significant association between use of Zoloft and either suicidal ideation or suicidal behavior in depressed pediatric and adolescent populations."[32] After reviewing Pfizer's studies of Zoloft in pediatric populations, the FDA's Office of Pediatric Therapeutics concluded in 2003 that no safety signals called for FDA action beyond ongoing monitoring of adverse events.[33]

Conclusion

Pharmaceutical decision-makers expect market and industry turbulence, but they were particularly constrained in 2005 by the confluence of regulation, distrust, monitoring technology improvement, medical and ecological studies, costly company errors, economic decline, and prohibitive R&D investment requirements. What could green chemistry offer within that context, if anything?

Yujie Wang made last-minute changes to her priority list of recommendations and saved the slide presentation to a Zip® drive. It was time to head down the hall to the executive committee meeting.

[30] U.K. Set to Ban Antidepressants for Children. *AFX International Focus.* December 10, 2003.

[31] *AFX International Focus.*

[32] Pfizer Inc., 8K Filing and 2003 Performance Report, Exhibit 99. January 22, 2004.

[33] Pfizer Inc.