A BRIEF HISTORY OF PFIZER CENTRAL RESEARCH*

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Pfizer Inc. celebrated its 150th anniversary in 1999. I will attempt to present a thumbnail sketch of the history of this company and of how it became the global pharmaceutical giant it is today. My special emphasis will be on the Central Research Division and the key role it played in the history of Pfizer Inc.

Two cousins, Charles Erhart, a confectioner, and Charles Pfizer, a chemist, were both in their mid-twenties when they came to the United States from Germany in 1849. They were the first of the innovative entrepreneurs that later came to be the standard for employees of Pfizer Inc. With $2,500 of their own money and a $1,000 mortgage, they set up shop in a two-story brick building on Bartlett Street in Brooklyn, New York. Initially, they sold high quality chemicals like santonin, a major treatment for intestinal worms that was a prevalent human disease in those days. Pfizer, the chemist, prepared this high-quality chemical and Erhart, the confectioner, flavored it to make it more palatable. Through their combined efforts it became a very successful product for the little company. This represented the first team effort at Pfizer—a technique that would be utilized extensively in the coming years. Within ten years the cousins were importing chemicals like mercurials, camphor, boric acid, tartaric acid, and citric acid extracted from lemons. They provided cream of tartar, iodine, and morphine during the Civil War, and their business grew rapidly. By 1865 they achieved $1.4 million in sales and employed 150 workers.

Charles Erhart

Through the late 1800s and early 1900s Pfizer Inc. expanded steadily but with no big spurts in growth. From 1917 to 1929 James Currie, Pfizer's first research chemist, developed a process for producing citric acid by fermentation of sugar. Currie came from the Department of Agriculture, where he was trying to produce an American brand of Roquefort cheese by fermentation. He was not successful. He then tried to ferment sugar to produce oxalic acid but again failed. However, he noticed an interesting byproduct in this fermentation: citric acid. Currie contacted Pfizer, related his finding, was hired, and, with his assistant Jasper Kane, eventually developed a large-scale fermentation process for citric acid. This process, called SUCIAC (sugar to cit-

ric acid conversion), was developed in response to the short supply of citric acid because of the high cost and variable supply of lemons from abroad. The fermentation process for citric acid was never patented, but it was kept a company secret.

In 1923 Jasper Kane made a major breakthrough in the citric acid fermentation process. He found a way to use molasses as a substrate, instead of the more expensive refined sugar. By 1929, through Pfizer's use of the new process, lemons were no longer needed for making citric acid; and citric acid production at Pfizer, all via fermentation, totaled 10 million pounds, with the product taking over almost the whole market at that time.

In addition to citric acid, another major fermentation success for Pfizer involved the production of penicillin on a commercial scale. The story of Alexander Fleming and his accidental discovery of penicillin in 1927 is a familiar one. Fleming's discovery might have remained a laboratory curiosity if a practical, large-scale production method had not been found. World War II increased the urgency for producing penicillin in quantity, but large-scale penicillin production could not be developed in war ravaged England. So Pfizer, in 1941, was asked by the US and British governments to accomplish large-scale penicillin production by means of deep tank fermentation. Merck, Lederle, and Squibb were also asked to join in this effort, with all the companies required to share their findings.

Initially, Pfizer used shallow trays for the fermentation process, producing just 24 milligrams (40,000 Oxford Units) of penicillin in 1943. Then Pfizer made a risky decision to commit $ 3 million for a deep-tank fermentation plant, which opened in a converted ice plant in March, 1944. By switching to a new penicillin mold (derived from cantaloupes) and using corn steep liquor in the broth, Pfizer scientists increased yields of penicillin from the deep-tank process dramatically.

By 1944 Pfizer was a world leader in producing penicillin by fermentation, actually supplying 90% of the penicillin to US troops who landed on D-Day, June 6, in France. For this effort Pfizer earned the "E" award for excellence in war production. By December, 1944 Pfizer was producing 125 *billion* Oxford Units of penicillin, with all of Pfizer's technology being shared with the other companies in the penicillin effort. Consequently, so much penicillin was produced that prices fell from 20 dollars to 20 *cents* per 100,000 Units. Penicillin, which saved so many lives in World War II, was not sold under a Pfizer label. Later, Pfizer produced streptomycin from fermentation with cultures supplied by Selmen Waksman. The scaled-up process eventually produced 3200 kilograms per month of this important antibiotic.

Charles Pfizer

At about this time, a soil sample screening program was established at Pfizer to search for even more potent antibiotics. This led to the discovery of a new class of antibiotics, the tetracyclines, in the Lederle laboratories in 1948. By 1950, the structures of the tetracyclines were elucidated by a Pfizer research team working with R. B. Woodward of Harvard. Meanwhile, Pfizer research uncovered PA-76, (Pfizer antibiotic, 76th sample), later named Terramycin, from soil samples. This agent was effective against 100 infectious organisms. Pfizer Inc. had total sales of $60 million in 1950, the year this fermentation product was approved by the FDA in less than six months. Then a key decision was made. Pfizer President, John Smith, told his successor, John McKeen, (who had joined Pfizer in 1926 and later rose to become the company's Chief Executive Officer), "Let's sell Terramycin ourselves; go into the pharmaceutical business if we have to." That was a critical decision and a big risk, since Pfizer would be venturing into unknown territory and would also anger the major wholesaler customers who were previously sellers of all Pfizer products. The decision, however, was a financial success. Sales of Terramycin, the first pharmaceutical with Pfizer's name on the bottle, rose to $45 million in just two years and accounted for 42% of company revenues. At that time, 55 Pfizer salesmen were selling the new antibiotic.

Together with Wilber Lazier, Karl Brunnings hired the 1950s group of Pfizer scientists who were the next generation of innovators for the company. A new group of chemists joined Pfizer's research team in the early 1950s, some of whom later went on to hold key positions in the company. They began their careers, as did the present author, in 1957, working in a small laboratory in Brooklyn, New York. Among these chemists was Gerald Laubach, a chemist who came from M.I.T. and headed the synthetic medicinal section of Pfizer's research. Later he was to become president of Pfizer Inc. William McLamore was a chemist from Harvard University who later became the inventor of several Pfizer drugs, including Diabinese. Robert Feeney, from Yale University, played a critical role in establishing a licensing department for obtaining products like Procardia XL from external sources. Lloyd Conover came to Pfizer from the University of Rochester. He played a critical role in the synthesis of Tetracycline and later headed up the Sandwich, U.K. research site and then Pfizer's animal health research. Rex Pinson, also from the University of Rochester, rose to become head of Medicinal Research. Barry Bloom, a chemist from M.I.T., was named President of Pfizer Central Research when it became a separate global division in 1971. Eventually he was Pfizer's Corporate Vice-President for R & D.

By 1953 the Pfizer sales force had grown to 1300, and company sales in that year had risen to $127 million dollars. Lloyd Conover succeeded in the chemical modification of chlortetracycline to produce the antibiotic Tetracyn, which was marketed in 1954. Now, with two major antibiotics to sell, McKeen opted to expand Pfizer's operations and sales into Europe, a risky decision for a small US-based company. But John McKeen had the vision to see the importance of markets outside the US. In 1957 the company opened a research laboratory in Sandwich, England with 6 scientists on staff. This small laboratory has grown today to fill a very large research site in Sandwich and contributed some of Pfizer's major modern pharmaceuticals, such as Norvasc and Viagra.

In 1958 Pfizer launched Diabinese for treating diabetes; this drug was the first non-antibiotic, small molecule pharmaceutical from Pfizer. The long plasma half-life and convenient dosing regimen made this sulfonylurea a commercial success. In 1960, research operations in the US were consolidated in Groton, Connecticut. On 19 acres of land already owned by the company across the street from the fermentation manufacturing plant, a new research facility was built in order to consolidate the various R&D departments. Having all the key scientific disciplines on one site was correctly viewed as vital to facilitating communications and thus making drug R&D more efficient.

There were other important changes occurring. At that time the synthetic organic chemistry camp was vying with the microbiologist fermentation chemists to gain control of the future direction for research. Would the Pfizer Company remain a fermentation-based company or not? Would synthetic organic chemistry produce the Pfizer drugs of the future? The outcome of these questions would not be settled for several years.

In 1960 John McKeen set the seemingly impossible goal of $500 million in sales by 1965 ("5X5"). As an employee, I remember how wildly impossible this goal seemed, but it was achieved. That same year, Pfizer headquarters moved from Brooklyn to a new skyscraper in midtown Manhattan at 42nd Street and 2nd Avenue.

Under the leadership of Gerald Laubach, Vice-President for Medicinal Products, a revamped research organization became more productive through systematic, well-planned, and scientifically managed R&D procedures. The organization adopted a philosophy of mission oriented research. Laubach required specific goals for the science being done, and he emphasized the rationally designed organic chemical as a source for future medicines. This move also coincided with the beginning of the first move to utilize informal multidisciplinary teams assigned to specific projects. Over time, synthesis of small organic chemicals as potential drugs became the accepted philosophy for research, and fermentation-based research decreased significantly.

In the decade of the 1960s, the Kefauver-Harris Amendments dramatically increased the cost, time, and difficulty of developing new pharmaceuticals. Pfizer Inc., concerned about its future as a pharmaceutical company, responded by diversifying into almost 30 nonpharmaceutical businesses. These included buying Barbasol shave cream, Desitin ointment for diaper rash, Pacquin hand cream and Coty cosmetics. Pharmaceutical research was continuing at Pfizer, however, with some successes during that period. Products developed during the 1960s and 1970s included Renese, a diuretic, the Sabin polio oral vaccine, which Pfizer produced on a commercial scale, Vibramycin, an antibiotic, Navane, an antipsychotic, and Sinequan, for depression.

In 1971 Central Research was formed as a separate, worldwide organization with centralized management out of Groton, Connecticut. This reorganization further improved the efficiency of Pfizer's R&D, although the R&D budget was still quite small compared to that of competitors, only about 5% of corporate sales. Groton was a small site with only a few chemists, biologists, metabolism chemists, and clinicians among the few hundred employees, a laboratory for bulk chemical materials, and a library. Barry Bloom was chosen to head the centralized management of Pfizer Research worldwide, while Sandwich was reorganized under the leadership of Lloyd Conover. New research management in Groton set focused goals, coordinated all projects, and held regular reviews of the growing R&D portfolio by a single group of research managers. The company experienced significant growth in sales in the 1970s from under $1 billion to almost $3 billion, but with almost flat R&D budgets and staffing. There was still concern among some Pfizer Corporate leaders about the wisdom of becoming mainly a pharmaceutical company and about investing too heavily in R&D. There were also some disappointments within R&D, such as failure of potential major products at late stages of development. These included Tolamolol, an antihypertensive, and Tibric Acid, a cholesterol-lowering agent. A successful antihypertensive agent, Minipress (Prazosin), was launched in 1976, however. Despite these relatively lean years of research productivity, Jack Powers, Chief Executive Officer from 1965 to 1972, strongly supported investing in R&D, even when corporate funds were limited. He recognized that Pfizer needed to support research as an investment for the future. Powers retired in 1972, appointing Gerald Laubach as President and Edward Pratt as Chief Executive Officer and Chairman of Pfizer Inc.

Pfizer's major product in the 1980s was Feldene, a drug for arthritis. The company's entry into arthritis research began in the 1960s with a team of two individuals, Ted Wiseman and the present author. Before success was achieved, a five-year research project was needed to identify an appropriate drug candidate, and then more than a decade to do extensive clinical trials and to select the best of the newly discovered oxicams and to secure its approval. The length of this project derived mainly from our determination not to follow the existing structural leads, then mainly carboxylic acids. Our goals raised the hurdles for the project, but in the end afforded a superior product from a medical and commercial point of view. The Feldene project was started in 1962 and concluded in 1982 with the US launch of the product—a 20-year period, about half the span of my career. It is not unusual for a project to require this length of time. For example, the project to produce Diflucan, a major antifungal agent from Pfizer, also took 20 years from the start in 1970 to the launch in 1990. Feldene became Pfizer's largest selling drug product at the time, with peak annual sales of up to $700 million by the late 1980s. This contributed significantly to corporate sales which more than doubled from $2.5 to $5.7 billion. The success of Feldene apparently convinced Pfizer's leaders that pharmaceutical research had a future and could lead to very successful commercial products.

Ed Pratt, Chief Executive Officer from 1972 to 1992, was a strong supporter of R&D during this period. He recognized the need to raise the R&D budget from the $50-million level (5% of sales) when he became CEO in 1972 to the 15-20% of sales needed to make the research organization a strong force and to build for the future. This daring investment in the 1970s transformed Central Research and laid the groundwork for Pfizer to become a productive research organization in the 1980s and 1990s. Feldene's clinical studies, the Zithromax project, and the Norvasc and Diflucan projects had their origins in the 1970s. Increasing R&D investment was a risky decision at a time when the pharmaceutical industry was under great pressure from the regulators. Eventually, Pratt spent a total of $6 billion on Pfizer's R&D during his tenure. As company annual revenues grew from over $1 billion in the 1970s to $7 billion in the 1990s, R&D funding increased from $8 million in 1971 to $179 million in 1981 and then to $757 million in 1991.

The growth of Central Research at all its worldwide sites created its own set of challenges, since increasing size brought increasing managerial problems. How does one manage such a large complex worldwide organization? Communications became more challenging; keeping the larger organization focused on the major goals became a problem. One solution involved formation of a senior management committee, the brain child of Walter Moreland and John Niblack, with the support of Barry Bloom. In this system both discovery and development are highly focused, goal-oriented, and managed by teams of scientists who report to a small group of senior managers. In the discovery phase, each research project has an operating plan with clearly defined goals, timelines, and milestones. The plan for the project is endorsed by management and reviewed regu-

larly. The latest technology is employed in order to make discovery efforts as efficient as possible. In the drug development phase, a similar group of senior managers from key departments regularly reviews the status, plans, and problems of each of the development projects. This management group hears the recommendations of the project teams and then makes the decisions on large expenditures, project terminations, and prioritization of projects.

In 1986 the present author helped to organize a project management group in Central Research and to establish the matrix team system. This was not an easy change in Pfizer's culture, but eventually the team environment for developing drugs gained acceptance. The Early Candidate Management Teams (ECMTs), led by scientists, manage a drug development project up to the start of Phase 3 clinical trials. The teams are made up of about 8 members from the key technical disciplines involved in the development project. These teams generate the pre-IND data and carry out Phases 1 and 2 in the clinic. Later, cross-divisional Global Development Teams (GDTs) plan and govern Phase 3 trials needed for NDA filing.

Pfizer's 42nd Street, NYC, World Headquarters Building

The productivity of Pfizer's own research and its licensing efforts increased dramatically in the 1980s and 1990s. Modern products launched by Pfizer in this period include: Feldene, an antiarthritic; Procardia XL, an antihypertensive; Unasyn, an injectable antibiotic; Zoloft, an antidepressant; Zithromax, an antibiotic; Zyrtec, for treating allergies; Norvasc, an antihypertensive; Diflucan, an antifungal agent; Lipitor, a cholesterol-lowering agent; Aricept, a drug for Alzheimer's Disease; Trovan, an antibiotic; Viagra, for erectile dysfunction; and Celebrex for arthiritis. During this same period two major potential agents failed in the development stage: Sorbinil was lost in Phase 3 because of a rash problem, and tenidap was withdrawn after filing because of a perceived effect on bone density. Such is the risky nature of pharmaceutical research. Tens of thousands of compounds are synthesized, and millions of tests are run annually, ultimately to bring 12 to 18 compounds into development, from which one product per year is likely to reach the marketplace.

Today the current leaders of Pfizer's R&D are George Milne as Central Research President and John Niblack as Vice-Chairman, Pfizer Inc. They are setting a new direction for Pfizer in the modern age of pharmaceutical research that will carry the firm into the 21st century. Major expansions are underway at Pfizer research sites worldwide. A total of more than one million square feet of R&D laboratory space is being added to these global research sites. Under the current Chief Executive Officer, William Steere, R&D annual investment has grown to over $2 billion. The corporation has sold the divisions that no longer fit into the core health care businesses: for example, the minerals operation, the Coty cosmetics business, and the Food Science group.

So the corporation has expanded dramatically in almost five decades. As the R&D budget has grown to over $2 billion, the R&D staff has increased to over 6,000 people worldwide. The acceleration in growth of the staff and in funding for R&D during the 1980s was made

possible by Feldene sales. Later, sales of other successful products permitted even faster growth in R&D in the 1990s. As a result of past R&D successes, Pfizer currently has strong corporate sales from major, important pharmaceuticals that will be under patent until beyond 2004-2006. In addition, a strong pipeline of future new products at various stages of development and significant growth in R&D, both in facilities and people, combine to make Pfizer Central Research a major force and a critical factor in the future success of the company. The innovative, entrepreneurial spirit initiated by the team of two cousins in 1849 has led to a giant organization with almost 50,000 individuals working in teams on five continents, a company where innovation and entrepreneurship are the lifeblood for the future.

The author's view of all this, from over 40 years of observing the growth of Pfizer Central Research and the parent company, Pfizer Inc., is that the success is due to the efforts of thousands of dedicated employees led by a relatively few visionary leaders. Their combined efforts brought us to where we are today and will lead us into a bright future.

REFERENCES AND NOTES

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