

## THE METAMORPHOSIS OF SMITH-KLINE & FRENCH LABORATORIES TO SMITH KLINE BEECHAM: 1925-1998\*

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The history of SmithKline Beecham is a wonderful example of the American success story: humble beginnings; hard work; a good reputation; growth; mergers; modest success; disappointments; breakthroughs; and ultimately, great success! But its previous successes have not made this company complacent, for today it is also an excellent model of an evolving, global pharmaceutical company.

This paper will cover many aspects of SmithKline, but the focus will be on the development of four products: “Benzedrine,” “Thorazine” (chlorpromazine), “Dyazide” (a combination of triamterene and hydrochlorothiazide), and “Tagamet” (cimetidine). These successes demonstrate the importance of research, as well as of marketing, but they also underline the importance of good people who are dedicated to their work and to the betterment of society. This story of a business is fundamentally a human story.

### In the Beginning

Although the Research Division was established in 1925, we must begin our story in 1830, when John K. Smith

founded a small apothecary shop on North Second Street in Philadelphia. His brother, George, joined him in 1841, and they formed John K. Smith & Co. The business grew and soon had a reputation for fine, pure products and became a leading drug wholesaler. Four years later, when John Smith died, George continued to build the company’s reputation. He was known for catering to the exact requirements of physicians, and for using methods that were quite advanced for his time. George took orders from as far away as central Pennsylvania and New Jersey. It was not unusual for other dealers to make semi-annual visits to his store to

place orders that would last for six months. By 1855, George Smith had not only expanded his store but had opened a second shop at 149 North Third Street.



Employees at the Cherry Street laboratory of Smith, Kline & Company in Philadelphia. Although the company was founded as a wholesale-retail business, in the 1880s it founded a small manufacturing laboratory to produce a few staple products. *Photo courtesy SmithKline Beecham.*

In 1865, Mahlon N. Kline, an ambitious young bookkeeper, joined the business. Together they continued to emphasize the purity of their manufactured products, with guaranteed quality. Kline soon sought a greater challenge and moved into sales, where he gained many new accounts. He also began to attend the Philadelphia College of Pharmacy, so that he would understand more of the business. A decade later he became a partner, and the company was renamed Smith, Kline & Company.

French Richards & Co., another well-established Philadelphia wholesaler, was absorbed by Smith, Kline & Co. in 1891, and the new company was named Smith, Kline and French. In due course, SK&F became Philadelphia's leading drug house, with hundreds of products—from tonics to medicines and liniments to perfumes. Furthermore, SK&F had established a pharmaceutical laboratory, where "Eskay's Neurophosphates" were developed, products which helped to facilitate the company's rapid growth. In 1893, SK&F instituted even stricter standards of quality and purity for its growing group of products, emphasizing its concern for providing exceptional quality to its customers. By the end of the nineteenth century, SK&F had expanded not only to a six-story building on Arch Street, but also into two adjoining buildings.

### A Focus on R&D

An important turning point came in 1925, when the Research Division of SK&F was established with the hiring of Dr. Fred P. Nabenhauer, an organic chemist. (He was the second person hired to conduct research, ultimately retiring in 1955. The first chemist, Dr. William L. Long, left the company to attend medical school, but later returned to serve for many years as Director of the Research and Development Division. He was one of the guiding lights in the advancement of research at SK&F.) Thus began the company's focus on research and development. In 1926 the first product from organic chemical research was "Oxo-ate B" (calcium *o*-iodoxybenzoate), designed to relieve swelling and muscle spasms in arthritis and rheumatism. This was followed in 1929 by "Benzedrine," an amphetamine designed to alleviate the symptoms of nasal congestion, hay fever, colds, and other upper respiratory conditions.

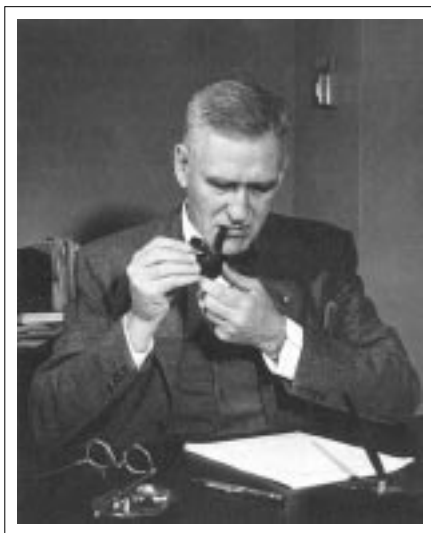
SK&F, led by Dr. Nabenhauer and later joined by Dr. George Connit, was conducting research on amphetamines at the same time as a California chemist, Dr. Gordon A. Alles. Dr. Alles believed that amphetamines

would make a good synthetic substitute for ephedrine, which had previously been used to treat asthma and nasal congestion. Based on his own experiments, Dr. Nabenhauer independently recommended amphetamines for the relief of nasal congestion. When SK&F became aware of Dr. Alles' research, they proposed a cooperative alliance for its development. By 1932, "Benzedrine" had become SK&F's first really big product. Much of the money made from "Benzedrine" was returned directly into research, and the company began to expand. Shortly thereafter, in 1934, Dr. Rudolph H. Blythe, a pharmacist, arrived on the scene to organize the Pharmaceutical Research Section, which he directed until his retirement in 1966.

Glenn E. Ullyot was the third chemist to be hired, in 1937, joining some 225 fellow employees at an ill-equipped building (formerly an abattoir during the Civil War) at Delaware Avenue and Poplar Streets. Two very significant additions to the scientific team in the late 1930s were Dr. Edward J. Fellows, a pharmacologist, and Dr. Arthur E. Heming, a biochemist. They, together with Dr. Ullyot, were named Associate Directors of R&D in 1957. (When Ullyot retired in 1975, there were almost 13,000 employees.) In 1943 organic chemistry became one of a number of scientific sections in the rapidly mushrooming laboratory groups under the direction of Dr. Walter Kerr, a biochemist. By 1950, the organic staff, under the direction of Dr. Ullyot, numbered eighteen persons, including the following Ph.D.s: Paul N. Craig, James F. Kerwin, James W. Wilson III, and Charles L. Zirkle. These chemists, subsequently joined by Andrew Anderson, and Drs. Bryce Douglas, Bernard Loev, Irwin Pachter, Robert F. Raffauf, Blaine Sutton, and Joseph Weinstock, formed the nucleus of an ever-expanding research team.

While SK&F was conducting its research on amphetamines, it was discovered that they exert a significant effect on the central nervous system. In 1939, SK&F began to investigate potential modifications of amphetamines and found one that was twice as effective as "Benzedrine." Researchers started to explore possible medical applications; the result was "Dexedrine," brought out in 1944 and marketed as a mood lifter and appetite suppressor. It soon found other applications, however, including use as a treatment for narcolepsy and for the reduction of post-surgical effects of anesthesia.

After World War II, SK&F continued to grow, and the company recognized the need for better facilities. In 1948 construction began on a big, yellow brick build-



Francis Boyer. As Executive Vice-President of the company, in the early 1950s he helped to negotiate the deal with Rhône-Poulenc that enabled SK&F to license chlorpromazine. *Photo courtesy SmithKline Beecham.*

ing at 1530 Spring Garden Street. This was the former site of the Baldwin Locomotive Works and, before that, of Bush Hill, said to have been the home of Alexander Hamilton. (Today this building is used primarily as a manufacturing facility.)

The development of Spansules was the next big success in the parade of products at SK&F. Beginning in 1945, Dr. Harold A. Clymer began looking for a time-release mechanism. In 1949 the group leader, Dr. Donald R. MacDonnell, while shopping in a supermarket, happened to note a container of nonpareils, little chocolate discs covered with a pebbling of white granules. Why not fill capsules with granules coated with medication that would dissolve at different intervals? This device enabled the medication to release the required initial dose rapidly, and then to release gradually very small doses to maintain a therapeutic level for ten to twelve hours. The "Spansule" sustained release capsule, the result of seven years of research and over 35,000 man-hours, was first used for "Dexedrine" in 1952. It became most famous eight years later, however, as the "tiny time pills" in " Contac," the first all-day cold remedy and the company's best-selling cold medicine.

### The First Major Breakthrough

As a result of focused research on a substance with infinite possibilities, a new and exciting chapter in SK&F

history opened. The success demonstrated the skills and foresight of Francis Boyer, then Executive Vice-President of the company, who was bilingual in the French language, and Dr. Wesler Scull. Boyer and Scull went to France to investigate the licensing of a new drug known as chlorpromazine. It was a mysterious compound, with many properties. The French thought of it as a "potentiator," a substance which prolonged the action of other drugs. Although two other American drug companies had turned down this compound, SK&F researchers, led by Dr. J. Kapp Clark, later Director of Research and Development, wanted to study it. They confirmed the laboratory pharmacology reported by the French and in SK&F clinical tests it was shown that the drug was indeed effective. So, Boyer continued talks (in French!) with Rhône-Poulenc; in 1952, SK&F was offered the opportunity to license chlorpromazine. Although chlorpromazine was found to possess several possible medical applications, Dr. Scull, then Director of Development Research, felt that the most important application was its astonishing calming effect on violent mental patients. The drug actually rescued patients from their psychotic states and restored them to lucidity. Boyer and SK&F agreed to pursue the use of chlorpromazine in mental illness, and in 1954 "Thorazine" was approved by the FDA for use in nausea and vomiting, and in neuropsychiatry. Though Freudian psychiatrists initially resisted the idea of using chemical treatment, "Thorazine" and its sister drugs "Compazine," acquired from the same French company, and "Stelazine," were quickly developed as useful drugs and were widely adopted in mental hospitals. The last mentioned drug was prepared in a classical extension of developing on a "lead" compound in Dr. Ulliyot's Medicinal Chemistry Section, notably by Dr. Craig.

From the historical standpoint, chlorpromazine and the alkaloid reserpine are the two substances which encouraged a chemotherapeutic approach to mental illness. Dr. Ulliyot and Dr. Maxwell Gordon noted in their 1968 article in the *Kirk-Othmer Encyclopedia of Chemical Technology* (1):

...electroshock, insulin shock, prefrontal lobotomy, etc, were thought to be the answer when they were first introduced. But the relative undesirability of these treatments can be judged by the fact that in some hospitals today they are virtually no longer employed as routine measures in psychotherapy... In modern institutions today there is a marked absence of the restraining devices, cold packs, noise, agitation, and confusion that have always characterized the mental disease wards.

Thus, treating mental illness with drugs proved to be a far more humane method than electroshock therapy or prefrontal lobotomy. The result was a dramatic, widespread release of mental patients from state institutions. In the US the resident mental patient population dropped 4.8% between 1965 and 1966, and 19% between 1955 and 1966 (1).

### The Next Big Development

The next big development was in the field of diuretics, one which SmithKline entered in 1955. The goal was a safe, effective, orally active diuretic. After years of testing many compounds for diuretic activity by a team including Dr. Joseph Weinstock and led by Dr. Ulylyot, the FDA approved "Dyrenium" in 1964, almost three years after the government evaluation began. Soon after SK&F's entrance into the field of diuretics, Dr. David Wheatley noticed an article in the *British Medical Journal* which indicated that the same substance that gave color to butterfly wings also caused hyperplasia, enlargement of the kidney (2). Dr. Virgil Wiebelhaus, who joined the diuretic group in 1956, began to investigate this substance, a pteridine compound. For almost a decade, SK&F scientists tested various pteridine compounds. None was completely successful, however, until triamterene. The diuretic team had endured several years of research and two clinical failures, but its members were confident they were on the right course with pteridines. In 1958, preliminary tests on triamterene indicated that it had good diuretic properties, and by 1960, clinical trials had been initiated. Dyrenium was compounded with hydrochlorothiazide (HCTZ) to make "Dyazide." HCTZ, a member of the group known as thiazides, was then in use as a diuretic, but it had the potentially harmful property of depleting potassium from the human body. The new dual compound, however, overcame this problem.

Although SK&F's marketing staff was less than enthusiastic, "Dyazide" did extremely well; along with "Contac" it carried the company through some lean times in the late 1960s and the early 1970s, when the "Thorazine" patent expired and the price fell. In fact, during this period there were no new breakthrough drugs in the development stage, and the company was forced reluctantly to discharge 200 employees in 1969. There had been a discouraging venture into the unfamiliar field of cosmetics, aimed at the teen market under the brand name of "Love," and suntan products, "Sea & Ski."

### The Tagamet Story

Of the four primary products discussed in this paper, "Tagamet" became by far the most profitable. However, it has been said that, without the income from "Dyazide," there would have been no funds to support the research that led to "Tagamet." Developed in the mid-1970s by a team of British scientists including Dr. James Black, Dr. William A. M. Duncan, Dr. C. J. Durant, Dr. C. Robin Ganellin, and Dr. E. M. Parsons, all working at SK&F's laboratory at Welwyn Garden City, England, "Tagamet," also known as cimetidine, is a histamine blocker, an H<sub>2</sub>-receptor antagonist, which was designed to treat peptic ulcers and other gastrointestinal disorders. When he joined SK&F in 1969, Dr. Black already held a theory concerning histamines. He knew that they encouraged gastric acid production in stomach cells and believed that, through application of his previous work on beta-blockers, it would be possible to inhibit this production. His predictions proved correct; by pursuing this avenue of research, Dr. Black and his team were able to develop a receptor-specific antagonist for histamines. The histamine research was slow: in the first four years of work, Dr. Black's team synthesized over 200 compounds, with no success. In the meantime, SK&F was discharging employees. The directors in Philadelphia were considering shutting down the program but ultimately decided to give the British researchers a little more time. The British team did not disappoint Philadelphia! It soon identified a possible active compound. Although the first few efforts resulted in antagonists which were either too weak or too toxic, the third attempt was a success, and "Tagamet," the world's first H<sub>2</sub>-receptor antagonist, came into being (3). Introduced in Great Britain in 1976, it was released in the United States less than a year later. Almost immediately "Tagamet" became an extremely popular method of treating ulcers, not because it was more effective than other traditional antacids, but because when it was taken daily, it helped to prevent the recurrence of ulcers. Sir James Black received the Nobel Prize in Medicine in 1988 for his work on beta-blockers and H<sub>2</sub> blockers.

It should be noted that on November 24, 1997 in Harlow, UK and again on February 27, 1998 in King of Prussia, Pennsylvania, the discovery of histamine H<sub>2</sub>-receptor antagonists was designated as an International Historic Chemical Landmark, conferred jointly by The Royal Society of Chemistry and the American Chemical Society.

## The Continued Growth of SK&F

In 1973, the firm's name was changed to SmithKline Corporation and SmithKline & French Laboratories—carrying on the name so familiar for 82 years—was retained for the pharmaceutical division. The company was well positioned for expansion and growth. By 1982 a



Anti-infectives facility in Upper Merion, Pennsylvania.  
Photo courtesy SmithKline Beecham.

new \$48 million headquarters had been built in Philadelphia's Franklin Plaza and later, a large, modern research facility in King of Prussia, Upper Merion, a suburb of Philadelphia. The firm had also acquired Allergan, an eye and skin care business, and Beckman Instruments, a California-based company which specialized in diagnostic and measurement instruments. As a result, the company became known as SmithKline Beckman, a name it retained for almost a decade. Allergan and Beckman Instruments were spun off in 1989 when SmithKline Beckman merged with Britain's Beecham Group, forming today's SmithKline Beecham. This merger resulted in a company that is one of the world's largest research and development organizations, with annual sales of over 12 billion dollars. Today, SmithKline Beecham is recognized for its cutting-edge scientific research and its many successful product developments. Much of this success has been due to good management and excellent marketing. However, it is fundamentally the talented and hardworking individuals, the scientists dedicated to basic research, who have enabled SmithKline Beecham to become the company which today is known and respected around the world.

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