Fine Chemicals

There are hard times at the glamour end of the chemical spectrum.

RICK MULLIN

The fine chemicals segment covers a broad range of chemical products that predominantly serve two large markets—pharmaceuticals and agricultural chemicals, with pharmaceuticals accounting for about 60% of fine chemicals sales of about $70 billion in 2003, according to industry analyst Enrico Polastro of Arthur D. Little. Other markets include photography chemicals and, to a growing extent, electronic chemicals.

Fine chemicals are generally defined as low-volume, high-value products that are selected on the basis of specific molecular properties, unlike specialty chemicals, which are purchased for their functional characteristics.

In recent years, fine chemicals have been viewed as the glamour end of the chemical industry. Distinctly high-tech materials produced in relatively clean batch processes, fine chemicals are the building blocks of cancer drugs as opposed to soap or paint.

The risks attending fine chemicals production are steep, however. And competition is stiff. The final decade of the 20th century, in fact, culminated in a gold rush scenario in which a wave of specialty and commodity chemical manufacturers bought into what promised to be the big growth sector for years to come. The field became overcrowded just as pharmaceuticals headed into a slump. Major chemical companies such as Eastman Chemical, Honeywell, and Great Lakes Chemical retreated from their original visions for fine chemicals operations. The industry is still working through the capacity of the late 1990s.

Others, especially European firms such as DSM, Lonza, and Degussa, emerged, after some restructuring, to steer their fine chemicals operations toward the new growth sectors such as life sciences and biologics. Some admit their fine chemicals businesses are still precariously situated.

But the fine chemicals sector is to a great extent an arena for small producers. Carrying on a tradition dating back to the early alchemists, entrepreneurs—such as Ivan Villax, a Hungarian refugee who after World War II went on to establish Hovione with two partners near Lisbon, Portugal—have pioneered new businesses in parallel with their quest for breakthroughs in chemistry and innovation in process engineering. Business builders—like James Mack, who turned a sprawling chemical operations holding company, Cambrex, into a textbook case of how to grow a fine chemicals business through acquisitions—have defined distinct strategies to support chemistry-based contract service companies. Small companies have, at various times, thrived and struggled in regional markets, where an entrepreneurial environment spawned national fine chemicals industries in the 1950s.

A Growth Past

The history of the modern fine chemicals industry dates back to the late 1800s, when the early chemical industry evolved from dyestuffs and explosives into modern pharmaceuticals. By the end of the 19th century, retail druggists had, for the most part, ceased to formulate their own medicinal preparations. Specifically, coal tar chemicals advanced into drug applications, and commercial production of branded drugs burgeoned, especially in Europe. Many of the drugs and the chemicals used to make them were produced in Europe, primarily Germany. Among the first mass-produced and marketed drugs were aspirin and organoarsenic drugs to treat syphilis.

World War I sparked enormous global change and growth in the sector, largely as a result of Germany cutting its supply of medicines and medicinal chemicals to the United States. This, as well as the sharp spike in demand for fine chemicals worldwide, sparked an intense period of innovation and growth, with many chemicals, such as potassium permanganate and methylcodeine bromine, being produced in the United States for the first time. Much of this activity centered around New York and New Jersey.

Top: Mallinckrodt Chemical Works 75th anniversary ad, 1950, *Chemical & Engineering News*

Center: Cartoon, Eastman Kodak Co. ad, 1963, *Chemical & Engineering News*

BAKER AND BADER

Historically, two companies have been major sources of chemicals for chemists—the powders and potions that stock individual research laboratory shelves. These are the J. T. Baker Chemical Company and Sigma Aldrich. Older by far, J. T. Baker is celebrating its 100th anniversary this year. In 1904, John Townsend Baker founded the company in Phillipsburg, New Jersey. Baker had a simple axiom: "Chemists need to know and have a right to know the purity of the chemicals they buy." To this end, the company provided significant quality control innovations throughout the years, including reagent labels that provided "Actual Lot Analysis" as a guarantee of purity according to defined analytical methods based on standard test procedures available in technical publications.

In a different fashion, but with similar goals, in 1951, Alfred Bader, a research chemist bothered by problems with the supply of organic chemicals for research, founded the Aldrich Chemical Co. and the Alfred Bader Chemical Library, to supply small quantities of rare chemicals to individual researcher chemists. Bader pioneered a distinctive sales catalogue that included not only details of his products' physical and chemical properties and references to the literature, but also reproductions of masterwork paintings in his personal art collection. In 1975, Aldrich Chemical Co. was acquired by biochemical supplier Sigma to become Sigma-Aldrich. In 2004, Sigma-Aldrich Fine Chemicals purchased Ultrafine, a U.K. supplier of custom-manufactured active pharmaceutical ingredients (APIs).

Top: Alfred Bader, *Chemical & Engineering News*

Center: Baker ad, 1950, *Chemical & Engineering News*

Other regional hubs emerged, such as Basel, Switzerland. The United Kingdom and Germany coalesced efforts into state-run companies—Imperial Chemical Industries and Inter-nationale Gesellschaft Farbenindustrie (I.G. Farben), respectively.

The U.S. effort to meet demand for chemicals and medicines during the war advanced a process of government oversight and regulation of the industry. As the war progressed, wild swings in chemical prices, supply, and demand led to a meeting on April 17, 1917, of the Medical Section of the Advisory Commission of the Council of National Defense with 250 manufacturers of fine chemicals, pharmaceuticals, and medicinal preparations. This meeting formed the basis of cooperative work on regulating production for the war effort.

Drug Developments

Major drug companies are among those that began manufacturing chemicals that were no longer available via export from Europe. One of these companies, Merck, was also formed during the war, when the U.S. operations of E. Merck in Darmstadt, Germany, were forced to split from the parent company and incorporate as a separate entity in the United States. Merck began manufacturing ethylmorphine hydrochloride and apomorphine hydrochloride. Eli Lilly stepped in to fill the void created when the Germans cut off atropine, which producers in that country extracted from the European herb belladonna, the deadly nightshade. Lilly developed a new method of extracting the drug from stramonium, the roadside jimson weed, using Fuller's earth.

The war generally broadened the scope of activity for medicine manufacturers—Abbott Alkaloidal Laboratories, for example, changed its name to Abbott Laboratories in 1914 after branching into coal tar medicines.

There were, however, smaller chemical companies that predated World War I in the United States, such as Mallinckrodt Chemical, a firm started by Edward, Gustav, and Otto Mallinckrodt in 1867 to manufacture fine chemicals for medicinal applications in St. Louis. The firm also began producing chemicals for photographic film in the 1880s. Mallinckrodt, which became a specialist in anesthetic ether and barium sulfate for X-ray diagnostics, built a factory in New Jersey and warehouses in New York City before World War I. During World War II, the company opened sales offices in Philadelphia and Chicago.

The 1930s marked the beginning of a boom in research, with Abbott and E.R. Squibb & Sons opening new research centers. E.I. duPont de Nemours opened its Haskell Laboratory of Industrial Toxicology under Wolfgang F. von Oettingen, a former professor at the medical school at Western Reserve University, and his assistant, W. C. Hueper of the cancer research laboratory at the University of Pennsylvania. And Abbott, Merck, and G.D. Searle established research grants for university and other drug researchers.

The sulfa drugs, specifically sulfanilamides, in the period between the world wars had been synthesized by I.G. Farben, which routinely checked dye intermediates for their medicinal qualities. Sulfanilamide, an unattractive brick-red dye, for example, proved effective against streptococci. Sulfa drug production in the United States followed on initial research done at Johns Hopkins University.

After the War

The fine chemicals sector emerged from World War II with the wide range of chemicals that constitute the basis for modern pharmaceutical and agricultural chemical products. The field filled with small producers throughout Italy, Spain, Finland, and other countries in Europe where patent protection had not yet emerged. By the 1970s, distinctions in the market were being made between commodity chemicals, specialties, and the newly defined segment of fine chemicals, according to Arthur D. Little's Polastro.

With the debut in the late 1970s of an ulcer drug, Tagamet, at SmithKline, an important new facet of the industry emerged: contract custom manufacturing. Scrambling to meet demand for one of the first in a parade of blockbuster drugs coming from the top pharmaceutical companies, SmithKline contracted with Fine Organics, a small British fine chemicals manufacturer, and Lonza in Basel for production of the key intermediate. In the years ahead, Fine Organics would be purchased by Laporte Performance Chemicals, which was later bought by Degussa. Lonza would emerge as a leader in the custom contracting field.

Lonza's rise began with a bad bet in the 19th century. With a background in hydroelectric power production, Lonza pursued development of calcium carbide batteries and acetylene as portable power sources based on a conviction that electrici-

ty would prove impossible to transmit over long distances. Lonza found new applications for its chemistries in active pharmaceutical ingredients, as did its neighbor, Rohner, which grew from the stagnating dyes market into fine chemicals, and, a few miles away, Siegfried. A small pharmaceutical firm, Siegfried cut back to its core competence of developing and manufacturing active pharmaceutical ingredients (APIs) in the 1980s.

As the blockbuster era in pharmaceuticals progressed, cycles in the economy pushed a range of major chemical companies—many of which were pruning their portfolios in the 1980s and looking for investments—to pursue pharmaceutical chemicals. Most dropped out of the sector in the downturn of the early 1990s. This process repeated itself in the late 1990s. With the specialties sector no longer promising the rate of growth it had in the previous decade, producers such as Eastman Chemical, Honeywell, and Great Lakes moved "downstream" in hopes of boosting revenues. A spate of acquisitions was followed by a round of investment in new capacity.

Major acquisitions included the purchase of ChiRex by Rhodia, of BTP by Clariant, and of PFC by Honeywell. Solutia bought AMCIS, and Degussa bought Laporte. Eastman increased its capacity for chiral and combinatorial-based synthesis reactions based on its epoxybutene capabilities via a technology agreement with Oxford Asymmetry.

In nearly every case, however, plans on the part of diversified producers fell short of expectations. Some of the acquired companies were divested; others showed mounting losses. A major capacity expansion and stagnating markets combined to produce a 20% overcapacity in fine chemicals production.

By 2000, another source of pressure on the market emerged in the form of competition from India and China. While fine chemicals contract manufacturers in this region were long considered a threat to Western producers, advances in the capability of Asian firms and shifts in patent laws, especially in India, turned up the heat. India and China now figure prominently on the radar screens of U.S. and European producers.

Despite the downturn and mounting pressure in recent years, manufacturers have continued to stake out growth spots, some betting that small niche players have a chance to grow even under tough conditions. Several firms, for example, have identified a growing market for high-potency pharmaceuticals. Solutia and Helsinn are among the firms that have invested in building specialized facilities to accommodate their manufacture—in both cases setting up operations in Switzerland.

In general, investment has continued throughout the sector, with many companies claiming they are gearing up for a market recovery. Rohner, the fine chemicals wing of MG Technologies' Dynamic Synthesis chemicals unit, for example, debuted a $51 million, eight-story fine chemicals plant, complete with polished oak floors, in Basel. Pharm-Eco in Devens, MA, is spending $10 million developing a 160,000-square-foot research, manufacturing, and office complex it purchased in 2000. Pharm-Eco's parent company, Johnson Matthey, has been on a spending spree in fine chemicals over the past three years, in fact purchasing Pharm-Eco; Meconic, the parent company of Macfarlan Smith, in Edinburgh, Scotland; Cascade Biochem, a small producer of prostaglandin; and Synetix, which specializes in chiral catalysts.

As Pharm-Eco pushes ahead in its plans to achieve critical mass in API manufacture, Rohner has fallen behind in its schedule for bringing in work, losing at least one major contract to a pharmaceutical company that pulled production in-house. MG recently sold its chemical operations, including Rohner, to Rockwood Specialties Group, a company backed by equity investment firm Kohlberg Kravis Roberts.

A Downstream Future?

Several major fine chemicals companies, however, believe the future may be brightest one step further downstream—and to some extent outside fine chemicals. The production of large-molecule biologics from fermentation and mammalian cell culture processes has attracted Boehringer Ingelheim, Lonza, DSM, Avecia, Dow, and Cambrex. After several years of investment, most analysts believe the supply-and-demand situation has reached a kind of balance, with production efficiency improvement considered the next step in keeping up with the rising demand, especially for monoclonal antibodies.

Cambrex, which in many ways has been a model for building a pharmaceutical fine chemicals company through acquisition—the firm purchased several fine chemicals companies and worked toward building a brand in pharmaceutical intermediates and APIs throughout the 1990s—has repositioned itself as a "human health sciences" firm, targeting biologics, cell therapy, and other life science and biotech markets. In doing so, Cambrex formed a company from its nonpharma operations, Rutherford Chemicals, selling it to Arsenal Capital Partners earlier this year.

Overall, the fine chemicals sector now finds itself in a period of change, centered on advances in end markets, most notably the rise of biopharmaceuticals. Analysts are divided on future prospects, noting that the sector as a whole experienced negative growth last year. Major players, however, are optimistic that by attuning themselves to the trends in drug development, as well as trends in agricultural chemicals and electronic chemicals, they will erect growth platforms from which to respond to the needs of high-tech industries that are, themselves, adopting new materials and strategies for supply chemicals. ◆

Above: Fine chemicals, Commercial Solvents Corp. ad, 1950, *Chemical & Engineering News*