Chapter 7

The Chemical Industry

"Why, after so much promise . . . has the harvest in the chemical area been so thin? Three basic, interrelated reasons give rise to the shortfall: 1) false expectations, which 2) in turn tended to obscure the inherent limitations in the technology, and 3) led to underestimating the difficulty of competing with the power of organic chemistry and entrenched chemical manufacturing processes.

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INTRODUCTION

Biotechnology has a number of applications to chemical production. Clearly, it will be used to improve production of biochemical currently produced using fermentation, such as industrial enzymes. In addition, there are also limited applications to the production of fine chemicals currently produced synthetically. Chemical firms are beginning to invest in these obvious applications.

In the long term, biotechnology maybe important in the production of bulk chemicals and fuels. But there is limited investment in this field due to the relatively low price of oil and the recent restructuring of the chemical industry.

INDUSTRY CHARACTERISTICS

The chemical industry is one of the Nation's largest manufacturing industries, with 1990 shipments estimated at $297 billion (24). It employs over 1 million people, representing about 5 percent of U.S. employment in manufacturing (4,25). Yet, the largest chemical companies are European (see table 7-1).

The chemical industry produces a huge and ever changing variety of products. More than 50,000 chemicals and formulations are currently produced in the United States (24). Three-quarters of the industry's output is used within the chemical industry to produce more complex chemicals or is sold to other manufacturing industries. Only a quarter of output is sold to consumers, purchased by government, or entered into foreign trade (16).

The consumption of chemical products by industry gives these products a degree of anonymity because they usually reach consumers in altered forms or as parts of other goods. Basic, raw materials, such as crude oil, are transformed through a complex series of interlocking steps into intermediate chemicals (e.g., benzene and acetylene) and eventually into complex final products (e.g., plastics and fibers). Often, several possible routes of chemical synthesis, using different feedstocks, can be used to produce a final product. Because chemical processors can substitute different feedstocks or intermediates for one another, they have considerable flexibility in adjusting to changes in price or availability of raw materials. Finished products can also substitute for one another. Different plastics, for example, can be used as packaging materials. The ease of substitution among raw materials and finished products results in intense competition within the industry.

Driven by competition, manufacturers constantly explore new feedstocks and develop new products. The resulting diversity of the industry has made its definition difficult. The Department of Commerce divides the chemical industry according to product classes in its standard industrial classification (SIC) system (see table 7-2).

Frequently, however, the chemical industry is divided according to the intensity of research and development (R&D). Some segments of the industry produce standard, high-volume, low-value-added bulk chemicals, such as ethylene or sulfuric acid. Because the quality of these chemicals is high and

Table 7-l—World's Largest Chemical Producers

BASF (Germany)
ICI (United Kingdom)
Hoechst (Germany)
DuPont (United States)
Bayer (Germany)
Dow Chemical (United States)
Shell Oil (United Kingdom, The Netherlands)
Enimont (Italy)
Exxon (United States)
Rhone-Poulenc (France)
Union Carbide (United States)
Degussa (Germany)
Ciba-Geigy (Switzerland)
Solvay (Belgium)
Asahi Chemical (Japan)

SOURCE: *Chemical & Engineering News*, vol. 68, No. 45, 1990, p. 20.

Table 7-2-Sectors of the Chemical Industry

SIC Code	Industry
SIC 28	Chemicals and allied products
SIC 281	Industrial inorganic chemicals
SIC 282	Plastic materials, synthetic rubber, manmade fibers
SIC 283	Drugs
SIC 284	Soaps, cleaners, and toilet goods
SIC 285	Paints and allied products
SIC 286	Industrial organic chemicals
SIC 287	Agricultural chemicals
SIC 289	Miscellaneous chemical products

SOURCE: U.S. Department of Commerce, 1991.

consistent, these manufacturers compete almost entirely on price which, in turn, depends on the cost of raw materials and the development of new process technology. At the other extreme are higher value--added specialty chemicals, such as catalysts, food additives, and industrial coatings. The highest value--added products include pharmaceuticals and pesticides (described in chs. 5 and 6). Manufacturers of specialty chemicals compete by investing in R&D in an effort to develop superior new products to meet market needs.

BIOTECHNOLOGY APPLICATIONS

Biotechnology will be used within the chemical industry mainly in the production of chemicals currently produced through fermentation, such as industrial enzymes. There are more limited applications to the synthesis of complex chemicals and to the production of bulk chemicals.

Most of these applications will be developed to improve production processes used by major chemical companies. They will, probably, be introduced without the fanfare that has accompanied other biotechnology developments. The use of biotechnology in the chemical industry is publicized only when a problem arises (see box 7-A).

Fermentation Products

Some chemicals are currently produced by growing micro-organisms in large fermentation vats and isolating the products from the final fermentation mixture. Biotechnology can be used to improve yields of these chemicals.

Amino Acids

Amino acids are used mainly as food additives and animal feed supplements, but they have other uses as well. The sweetener Aspartame is made from two amino acids: aspartic acid and phenylalanine. The food additive monosodium glutamate (MSG) is probably the best known amino acid. The world market is estimated at $800 million and is growing at 3 percent annually, although the U.S. market is growing slowly or not at all (27).

The use of biochemistry and fermentation to produce chemicals has historically received a great deal of attention in Japan. Unlike Germany and the United States, Japan is resource-poor, lacking large deposits of coal and oil, the raw materials on which the chemical industry in the rest of the world was based; thus, Japanese firms have always had a financial incentive to explore alternatives. When Japan's Ministry of International Trade and Industry

Box 7-A—L-tryptophan and Eosinophilia-Myalgia Syndrome

The amino acid L-tryptophan has been widely available, mainly in health food stores, as a food supplement. It was often recommended as a treatment for insomnia, depression, and premenstrual syndrome. In 1989, ingestion of L-tryptophan was linked to an increase in the number of cases of a rare blood disorder, Eosinophilia-Myalgia Syndrome (EMS). In November 1989, the Food and Drug Administration (FDA) recalled all products containing L-trytophan as a major component, and in March 1990, the FDA extended the recall to nearly all products containing L-tryptophan. Over 1,500 cases of EMS and 27 deaths in the United States were eventually traced to several lots of L-tryptophan produced by a single company, Japan's fourth largest chemical firm Showa Denko. Lots of L-tryptophan associated with EMS contained small amounts of a contaminant.

Like many other amino acids, L-tryptophan had been manufactured by growing bacteria that produce L-tryptophan in large fermentation tanks and purifying the compound from the broth. In late 1988, however, Showa Denko made two changes in its L-tryptophan manufacturing process. It replaced its original strain of bacteria with a strain genetically engineered to enable it to produce more L-tryptophan; changes were also made in the purification process.

In October 1990, the contaminant associated with EMS was identified by Showa Denko scientists as an L-tryptophan dimer linked by ethylidene. The company announced that the contaminantt was not produced by the bacteria during the fermentation process but was formed during the L-tryptophan purification process.

SOURCES: Centers for Disease Control, "Update: Eosinophilia-Myalgia Syndrome Associated With Ingestion of L-Tryptophan—United States, through Aug. 24, 1990," *Morbidity and Mortality Weekly Report*, vol. 38, 1990, pp. 587-589; E.A. Belongia et al., "An Investigation of the Cause of the Eosinophilia-Myalgia Syndrome Associated with Tryptophan Use," *The New England Journal of Medicine*, VOL *323, 1990*, pp. 357-365; A.N. Mayeno et al., "Characterization of Peak 'E,' a Novel Amino Acid Associated with Eosinophilia-Myalgia Syndrome," *Science*, vol. 250,1990, pp. 1707-1708..

(MITI) targeted biotechnology in 1980, three research areas were specifically named: 1) recombinant DNA (rDNA), 2) mass cell culture, and 3) bioreactors. Although in the United States, the word "bioreactor" usually refers to large chambers used for mass cell culture, MITI defines bioreactors, more generally, as any fermentation vessel. The more-advanced research in bioreactor development, funded by MITI, emphasized the use of micro-organisms or immobilized enzymes for the production of fine chemicals. Since 1981, six Japanese chemical firms have participated in a government-sponsored joint research effort in this area (15,28). So far, this consortium has conducted research but has not produced any commercially useful products or processes (27).

Industrial Enzymes

Enzymes are biochemical catalysts. Of the approximately 18 commercially available in bulk, five are most important. These are amylases, which produce simple sugars from more complex ones, and are used in the starch industry; bacterial proteases, which digest protein, and are used in detergents; papain, for dehazing beer and tenderizing meat; glucose isomerase, for making high-fructose corn syrup; and rennin and chymosin, both used in cheesemaking (10). A variety of enzymes have been developed for other industrial uses. For example, one bacteria-derived enzyme, cellulase, which breaks down cellulose, the molecular base of cotton, has been used to soften new blue jeans as an alternative to harsh stone-washing (12).

The major producers of commercial enzymes are Novo-Nordisk (Denmark) which has about 40 percent of the market, and Gist Brocades (Belgium) which has about 20 percent of the market, followed by Rohm (Germany), Miles (United States), and Hansens (The Netherlands) (10). The current world market for industrial enzymes is over $650 million per year (27).

Biotechnology can be used to improve the yield of an enzyme through transfer of the gene encoding the enzyme to a micro-organism capable of producing the enzyme in larger amounts. Novo-Nordisk researchers, for example, identified a fungal, fat-digesting enzyme, lipase, that helps breakdown fats typically found in human food. To produce it in commercial amounts as a detergent additive, however, they transferred the gene from the fungus in which it occurs naturally (in small amounts), to a fungus that will produce lipase in higher quantities. A detergent containing this enzyme was first introduced in Japan (26).

But biotechnology can contribute more to the production of industrial enzymes than yield enhancement. The gene encoding the enzyme can be modified to encode an enzyme with altered characteristics. Research is being conducted to develop enzymes that are more stable in harsh solvents, are more heat resistant, or that react with different substrates. For example, one enzyme used in detergents, subtilisin, degrades proteins such as those found in blood or food stains. Because the enzyme is sensitive to bleach, a common ingredient in many detergent formulations, variants have been generated using biotechnology, that are more resistant to bleach than is the original enzyme (2).

Biosensors

Biosensors combine biotechnology with materials science and electronics to produce sophisticated monitoring devices. This is an area of active research throughout the world but especially in Japan (19).

A biosensor consists of two basic parts: one layer that responds to the presence of a specific chemical (e.g., a layer of enzymes that react with the chemical to be measured or antibodies that bind specifically to it) and a second layer that consists of a transducer that translates this specific interaction into electric signals proportional to the concentration of the chemical in the sample. The electronic part of the biosensor measures voltage, current, light, sound, temperature, or mass.

Currently, most biosensors are used to detect biological materials. Much research is directed toward the development of biosensors for diabetics, that could monitor glucose levels and control an insulin pump. But biosensors have many other potential applications in medicine and industry. Eventually, biosensors will be developed to detect cholesterol, narcotics, or substances associated with early disease diagnosis. In industry, biosensors will monitor and control industrial effluents, fermentation processes, and food quality. Biosensors will also be developed to monitor the presence of toxic substances in water supplies and organic solvents in air (1 1).

Most existing biosensors have drawbacks. They are bulky, need frequent calibration, and have a short useful lifespan. R&D is aimed at improvements in these areas, to eventually develop disposable biosensors and, for some applications, sterilizable biosensors.

Applications to Chemical Synthesis

Some chemicals are manufactured in a series of complex chemical reactions. Under certain conditions it might be practical to replace one or more of these reactions (those that are expensive or particularly difficult to control) with reactions controlled by enzymes, which are biochemical catalysts. Reactions controlled by enzymes have some advantages, e.g., they work at mild temperatures, they can often be used to perform more limited reactions, they can be used to produce chiral compounds, they are biodegradable, they require no organic solvents, and they are very reaction-specific. But these situations are limited. Enzymes, altered using biotechnology or not, are unlikely to make a big impact in this area in the new future (13).

Applications to Bulk Chemical Production

Although it is technically feasible to produce many high-volume, low-value-added chemicals through fermentation, these methods are not economically competitive with established petrochemical processes. This area is also unlikely to receive much R&D investment, as the major multinational firms have been decreasing their interest in bulk chemical production (17,20).

Photo credit: U.S. Department of Energy

Scientist mixes a chemical sample.

GLOBAL RESTRUCTURING

In the very long run, biotechnology may have a major impact in shifting the production of fuel and bulk chemicals from reliance on nonrenewable resources, such as oil, to renewable resources, such as biomass (14). There does not, however, appear to be much industrial interest in these applications, in part, because the international price of oil has remained too low to encourage investment in alternatives and, in part, because the chemical industry throughout the world has restructured during the last 10 years. As major oil companies have increased their bulk chemical production, chemical firms have decreased their share of the bulk chemical market and increased their interests in the production of specialty chemicals, pharmaceuticals, and agricultural products.

The industry's restructuring has been a strategic response to worldwide pressures, stemming from fluctuating oil prices, recessions, and increasing competition. Historically, the industry's annual industrial growth rate averaged two to three times the rise in Gross National Product (GNP). During the 1970s the industry began to decline worldwide. Industrial growth fell and became even with the growth in GNP (7). Chemical production decreased for a number of reasons.

- Most importantly, the industry had reached technological maturity. Innovation in products and manufacturing processes had declined. In addition, substitution of synthetics for natural materials had leveled off; for example, by 1970, synthetic detergents had taken 85 percent of the market for domestic and industrial cleansers (3).
- Manufacturers faced erratic fluctuations in the price of oil, which is important, both as a source of energy and as a basic feedstock, for the production of bulk chemicals. Oil supplied by the Organization of Petroleum Exporting Countries (OPEC) constituted about 80 percent of the raw materials used by the U.S. chemical industry (7).
- Chemical companies were also facing new costs, in the form of environmental protection regulations, particularly in the United States.

- New competition came from multinational oil companies diversifying into the production of bulk chemicals. These firms built petrochemical plants in Indonesia, Mexico, and the Middle East producing chemicals from natural gas and waste gases derived from oil processing and refining. Chemical companies in major industrial nations often had no sources of raw materials as inexpensive as those in oil-rich nations (1,3).
- The chemical industry was particularly hurt by the worldwide recession in the early 1980s. Demand for petrochemicals slumped, along with the profits of the chemical industry.

Chemical companies reduced operations in bulk chemicals, generally retaining production of chemicals in which they were market leader or in which they had a price advantage based on proprietary technology (7). Other operations were sold. Between 1981 and 1986, Dow sold more than $1.8 billion in assets and wrote-off most of its oil and gas business. Bulk, low-value chemicals once provided 61 percent of Monsanto's profits; the proportion shrank to 35 percent in a 4-year period. American Cyanamid once consisted of four roughly equal segments: medical, agricultural, chemical, and consumer products. By 1987, medical and agricultural products made up about 75 to 80 percent of its business (9). American fins, which had dominated bulk chemical production in Europe during the 1950s and 1960s, gradually withdrew, selling their assets to local firms (3).

During the same period, chemical firms expanded into the two sectors, pharmaceuticals and specialty chemicals, which continued to be quite profitable and recession-resistant. Most of this expansion came through acquisition. Major producers of agricultural chemicals have diversified into seed production, and chemical firms have also expanded their interests in advanced materials and instrumentation. Restructuring has been successful, in that industry profits recovered from the slump of the early 1980s. More recently, however, recession and rising oil prices once again have hurt the industry.

There are many examples of chemical industry restructuring and resulting investment in research-intensive fields. Since 1985, Monsanto, the St. Louis-based chemical firm, has shut down or sold more than 20 businesses that were largely producers of high-volume, low-value-added chemicals. They have, simultaneously, acquired firms producing specialty products, including pharmaceuticals, food additives, and detergent chemicals (22). Similarly, Dow's managers decided in 1978 to cut back on bulk chemicals and extend the fro's interests in specialty chemicals and related high-value areas. Dow acquired Merrill, a U.S. pharmaceutical firm, in 1981, and in 1984 it acquired an 84-percent interest in a small Japanese pharmaceutical firm, Funai Pharmaceuticals Co., Ltd. Dow has also expanded its interests in household cleaning products, polymers, and advanced ceramics (3). DuPont recently joined with Merck to form a new pharmaceutical firm. It has also joined with DNA Plant Technology in its FreshWorld venture, selling branded vegetable produce (3,8). Rohm & Haas has invested in agricultural biotechnology firms in the United States and Belgium.

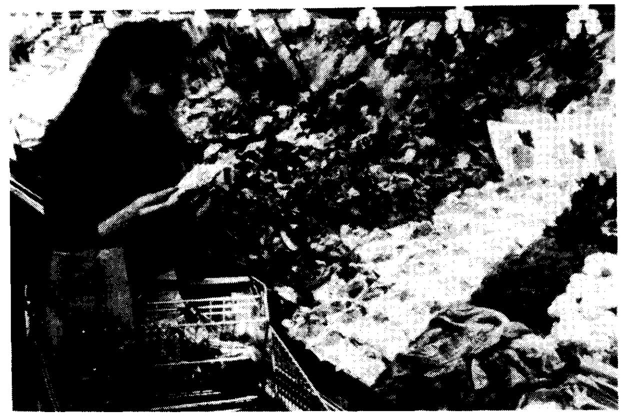

Photo credit: DNAP

FreshWorld, a joint venture between DNA Plant Technology and DuPont, has been marketing VegiSnax brand carrot and celery sticks.

Restructuring in Europe and Japan had similar results. The major European chemical firms have redistributed their assets and, like American firms, have invested heavily in R&D-intensive products (8). For example, Hoechst, a large German chemical manufacturer, purchased Celanese in 1986, acquiring its advanced facilities for the production of fibers, chemicals, and plastics. Hoechst also placed a major emphasis on the production of pharmaceuticals, which represent 17 percent of its world sales (3). Hoechst was also one of the earliest big investors in biotechnology, providing $70 million to Massachusetts General Hospital in 1980 in exchange for the right to license research results and to send its own scientists for training. The British firm ICI has developed its presence in agricultural products

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through acquisition of seed companies and by expanding its existing research in plant biology (6).

In addition to acquiring pharmaceutical and agricultural firms, some American and European chemical companies have invested heavily in internal research in the life sciences. Among these are: Monsanto, DuPont, Lubrizol, Royal Dutch-Shell, ICI, and the French companies, Elf-Aquitaine and Rhone-Poulenc (18). The petrochemical company, Lubrizol, acquired the plant biotechnology firm, Agrigenetics, in 1988.

Although outright acquisitions of biotechnology firms are rare, other relationships between chemical companies and small biotechnology firms are quite common. DuPont, for example, has R&D, marketing, and licensing agreements with several small firms, including American Bionetics, Applied Biotechnology, BioTechnology General Corp., Cellular Products, Cistron, Genofit SA, Molecular Biosystems, and Synergen. American Cyanamid has agreements with Biotechnology General Corp., BioProbe, Cytogen Corp., and Molecular Genetics, Inc. European and Japanese firms have also contracted with or invested in many small U.S. firms specializing in biotechnology, but they have not fostered the development of similar small firms in Europe or Japan (21,23). A recent study has shown that chemical companies provided 63 percent of the research funds spent by the top 15 plant biotechnology firms in 1989. The leading investors were Monsanto (U.S.), Enimont (Italy), DuPont (U.S.), Sandoz (Switzerland), and ICI (U.K.) (5).

Global restructuring of the chemical industry in the last 10 years has resulted in investment in high-value-added products, such as pharmaceuticals, agrochemicals, and other specialty chemicals. As firms decrease investments in the production of low-value-added chemicals, it becomes less likely that research in biotechnology applications to biomass-based production will be funded by the private sector.

SUMMARY

Biotechnology has a limited role in chemical production. Production of some chemicals now produced by fermentation, such as amino acids, could be affected through improvements in microorganisms or production processes. Similarly, biotechnology can be used to improve yields of industrial and food enzymes isolated from microorganisms. In addition, biotechnology could be used to produce enzymes with altered characteristics. Biotechnology can also be applied to the development of enzymes that might be used to replace expensive or difficult steps in chemical synthesis. In all of these cases, however, the impact of biotechnology will be incremental and unheralded, resulting in improvements in productivity. Biotechnology is unlikely to be applied to the production of fuels or bulk chemicals in the foreseeable future, because it is not financially or technically competitive with current chemical methods of production (20).

The chemical industry's greatest impact on the use of biotechnology, however, is likely to have little to do with industrial chemical production per se. Indeed, its greatest impact may be the result of the industry's expanding investment in pharmaceuticals and agriculture. This investment has taken the form of increased in-house research and links with smaller research-intensive firms.

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